

Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

The first chapter in Volume 68 deals with *diseco*-nucleosides, i.e., with analogs of nucleosides in which there are two bond disconnections. This chapter represents the second of a trilogy of chapters by Professors El Ashry and El Kilany (Alexandria University, Egypt), in which they deal comprehensively with acyclic nucleosides. The first of the series appeared in Volume 67 and considers *monoseco* derivatives and the third and final chapter will appear in Volume 69 and cover *tri*- and *polyseco*-nucleosides.

The second chapter in this volume, "1,3,2-Dioxathiolane Oxides: Epoxide Equivalents and Versatile Synthons," is authored by Dr. B. B. Lohray and Dr. V. Bhushan of the Reddy Research Foundation, Hyderabad, India. These compounds are cyclic sulfates and, over the past seven or eight years they have become important intermediates in organic synthesis.

The next chapter deals with methylpyridines and other methylazines as precursors to bi- and polyheterocycles and is a joint contribution from Salford University, England, and the University of Kuwait, authored by Drs. F. A. Abu-Shanab, B. J. Wakefield, and Professor M. H. Elnagdi.

For the final chapter in this volume, we return to the chemistry of nucleoside analogs, which are so important in modern medicinal chemistry and the fight against viral disease. This chapter deals with *C*-nucleosides of the heteromonocyclic bases, covering not only the well-known pyrimidines, but a variety of other important heterocycles and is authored by Professor M. A. E. Shaban and Dr. A. Z. Nasr also of Alexandria University, Egypt.

ALAN R. KATRITZKY

Acyclonucleosides: Part 2. *diseco*-Nucleosides*

E. S. H. EL ASHRY AND Y. EL KILANY

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Alexandria, Egypt*

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This chapter is the second of a sequence of three chapters that appears in successive volumes of this series dealing with the chemistry of acyclonucleosides. The first chapter appeared in the previous volume [97AHC391] and dealt with *seco*-nucleosides (one bond disconnection). This chapter deals with *diseco*-nucleosides (two bond disconnections). The final chapter of this series will deal with *tri*-, *tetra*-, and *pentaseco*-nucleosides, as well as contain an appendix of the literature that appeared after the three chapters were prepared.

III. *diseco*-Nucleosides from Two Bond Disconnections

Acyclonucleosides that are considered under this type of disconnection are those resulting from omitting any two bonds from the pentose. There are seven such types.

A. 1',2'- AND 2',3'-*diseco*-NUCLEOSIDES (TYPE 2.1)

The most important member is the guanine analog. There are various modifications under this type of acyclic nucleoside.

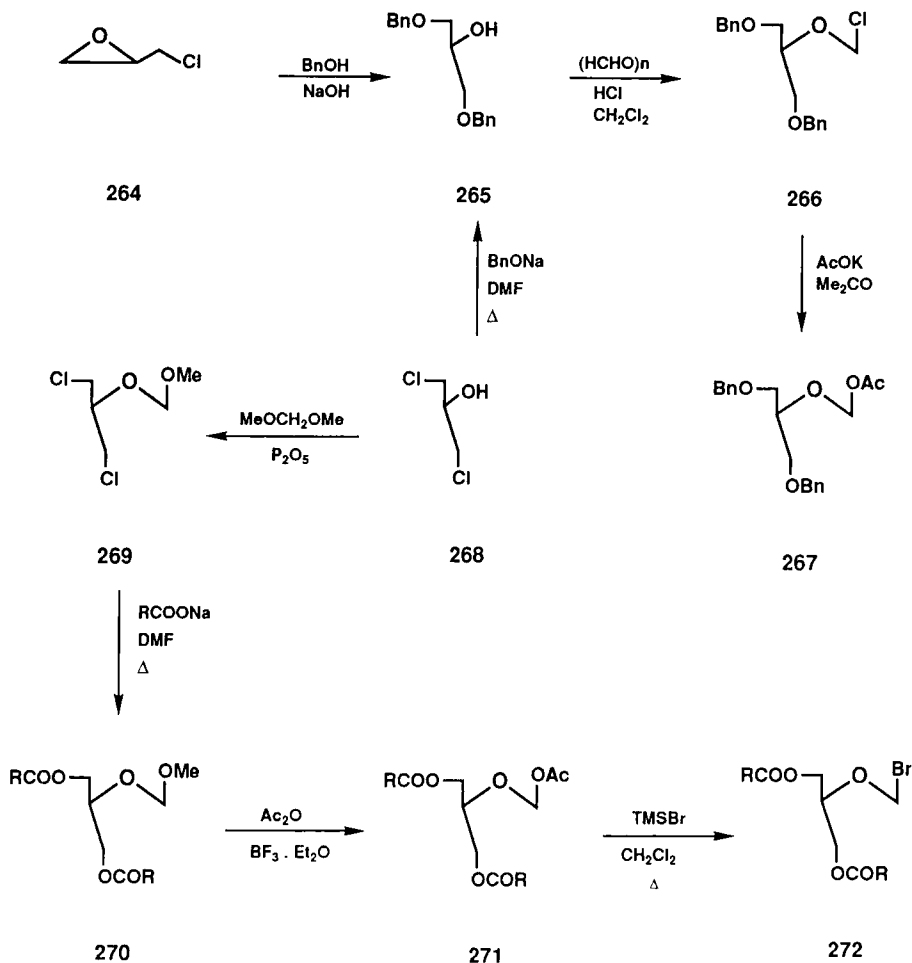
* Part 1 is in Volume 67 and Part 3 is in Volume 69.

1. General Methods for Construction

Most of these methods involve the alkylation of the heterocyclic ring by a suitable alkoxy alkyl halide. Further modification on the heterocyclic rings may sometimes be used on a preformed acyclonucleoside. Thus, the chloromethyl ether **266** was prepared from epichlorohydrin (**264**) by treatment with benzyl alcohol and aqueous NaOH to give 1,3-di-*O*-benzylglycerol **265** (83JMC759). Alternatively, **265** was prepared from 1,3-dichloro-2-hydroxypropane **268** (84CJC241). Chloromethylation of **265** gave **266**, whose treatment with potassium acetate gave 2-*O*-(acetoxymethyl)-1,3-di-*O*-benzylglycerol (**267**) (83JMC759). The choice of the hydroxy protecting groups must be made to avoid difficulties encountered with the removal of the benzyl groups during the subsequent steps, particularly in the cytosine series. Thus, the requisite acyclic chain **272** was prepared by commencing with 1,3-dichloro-2-propanol **268**. Methoxymethylation of **268** gave **269**, where this group served a dual purpose. It protected that position from a *trans*-acylation process in the subsequent step and furnished the backbone methyleneoxy unit whose methoxy group could be converted into the most suitable leaving group. Treatment of **269** with the desired acid salt in DMF gave **270**, whose acetolysis gave **271**, which converted it to the bromomethylester **272** (88JMC144).

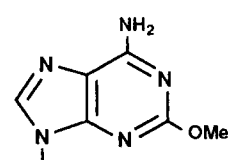
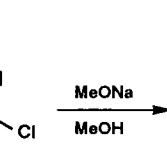
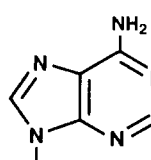
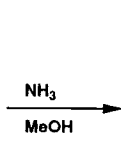
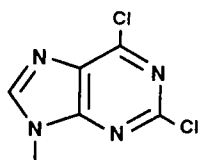
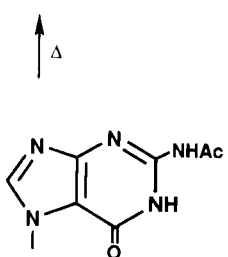
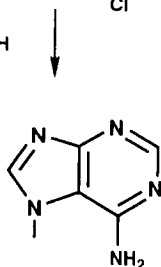
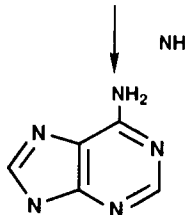
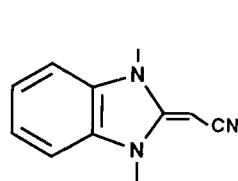
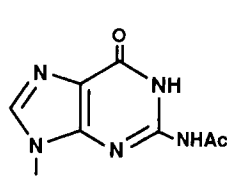
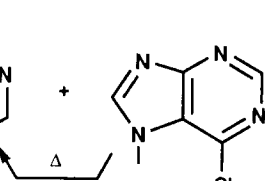
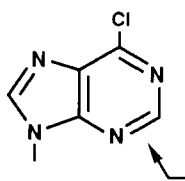
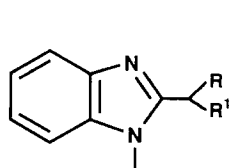
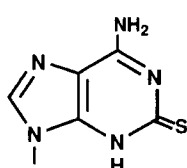
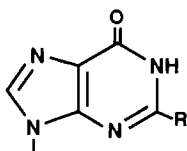
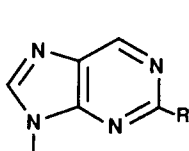
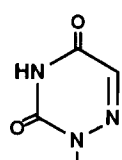
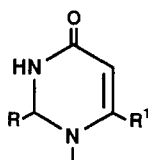
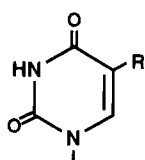
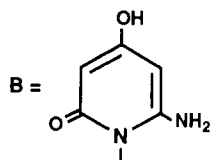
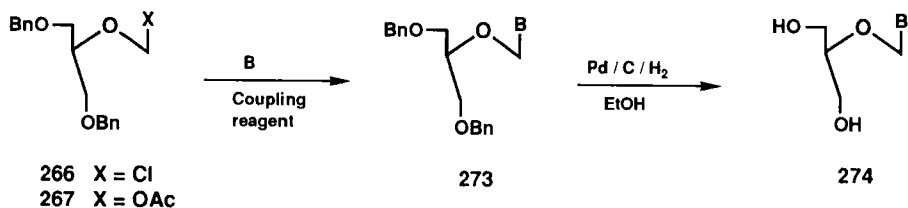
The synthesis was started by condensing the persilylated base with chloromethylether **266** (79JMC21; 82CJC3005; 84CJC16; 85JMC358, 85JMC971, 85USP4508898; 87MI4; 88MI2; 89MI8; 90GEP3906357). Both mercuric cyanide and tetra-*n*-butylammonium iodide (TBAI) were frequently used as catalysts in the coupling reactions. The latter catalyst has the advantages that it is less toxic, is required in smaller quantities, and involves reactions that are generally easier to manipulate during workup. Lithium bromide/TFA/MeCN was also used (88MI2). In the case of triazine derivatives, in addition to the major product, a minor quantity of the 4-alkylated isomer was obtained (91MI5). Direct or phase catalytic hydrogenation of **273** gave **274**, except in the presence of a halogen or nitro group when boron trichloride was used (84CJC16, 84CJC241; 85JMC358, 85JMC971; 87MI2; 93MI1). Attempted debenzylation with BBr₃ gave a 2-methoxymethyl derivative because of complex formation between BBr₃ and the C-2 oxygen. Nucleophilic substitution may have occurred at C-1' (N—CH₂—O) when the complex was quenched by the addition of MeOH (91MI5). However, the chlorine atom in position 6 of 6-chloro-Pu and 6-chloro-Gu could be hydrogenolyzed without any significant loss of the benzyl groups (84-CJC241).

In the case of purine derivatives, the N-7 isomers were obtained, in addition to the N-9 isomers; the N-7 isomers rearranged to the N-9 on



SCHEME 55

heating (84CJC2702). The 6-chloropurines could be converted to the corresponding methoxy or hydroxy derivatives by NaOH/MeOH/H₂O at room temperature and on heating, respectively. The 2-amino-6-chloropurines were converted to the 2-amino-6-methoxypurines and to the guanine analogs by reaction with NaOMe and NaOH/MeOH/H₂O, respectively (84CJC2702). In 2,6-dichloropurine, substitution of the 6-chlorine atom takes place preferentially, by which means another substituent can be introduced later at the 2-position [86IJC(B)823].



Coupling reagent

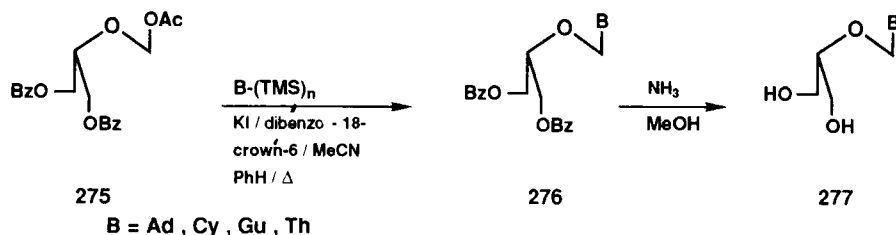
HMDS / $(\text{CH}_3)_2\text{SO}_4$ / Bu_4NI / CH_2Cl_2

HMDS / $(\text{CH}_3)_2\text{SO}_4$ / $\text{Hg}(\text{CN})_2$ / PhH

HMDS / $(\text{CH}_3)_2\text{SO}_4$ / CS_2 / MeCN

LiBr / TFA / MeCN ; Et_3N / DMF.

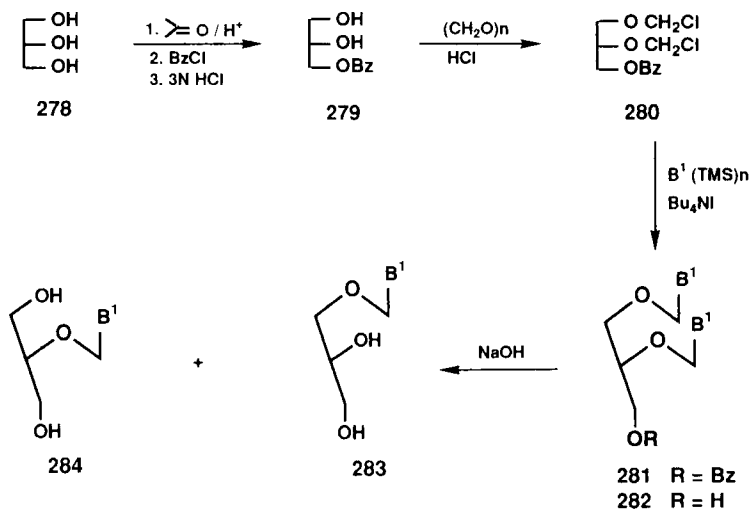
SCHEME 56



SCHEME 57

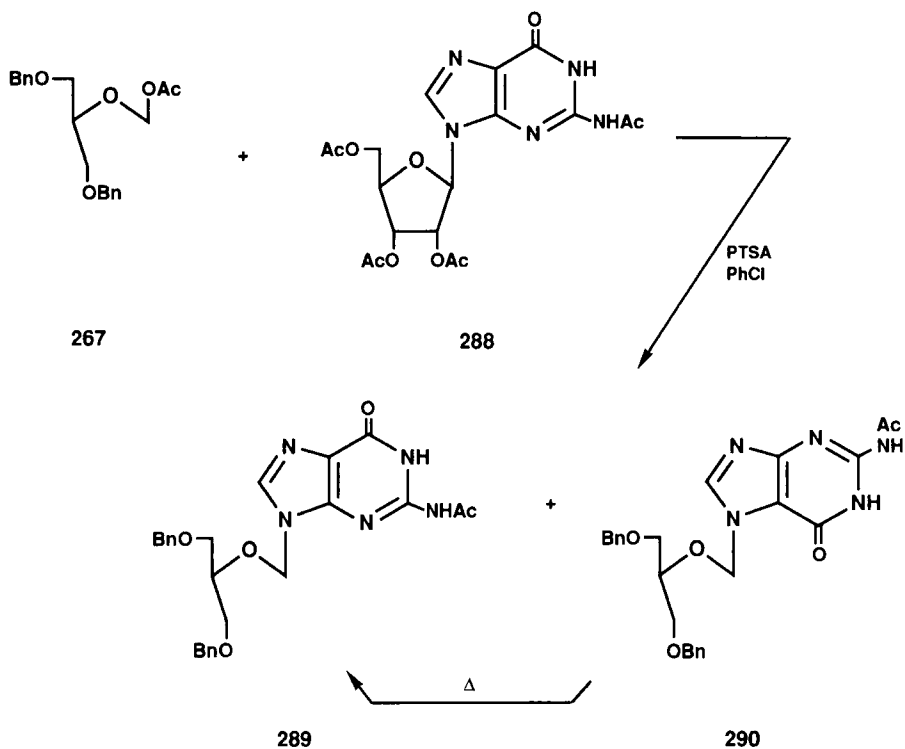
The synthesis of chiral acyclic nucleosides **276** utilizes the readily available protected acetoxymethyl ether of glycerol **275**, which reacted with silylated nucleobases under phase transfer conditions using dibenzo-18-crown-6 to give N-9 purinyl and N-1 pyrimidinyl acyclonucleosides. Removal of the benzoyl groups by methanolic ammonia gave **277** (88JMC144; 89TL6165).

The bis-chloromethyl ether **280** could also be used for alkylation. Thus, isopropylidenation of glycerol (**278**) followed by benzoylation and deisopropylidenation gave **279**, whose chloromethylation gave **280**. Coupling of the latter with silyl derivatives of bases gave **281**, whose deprotection gave **282**, whereas the use of sodium hydroxide led to a cleavage of one of the methyl ether linkages to give **283** and **284**. The former belongs to nucleoside analogs of type 2.2. Mixed derivatives of **282** were also prepared (86MI2).

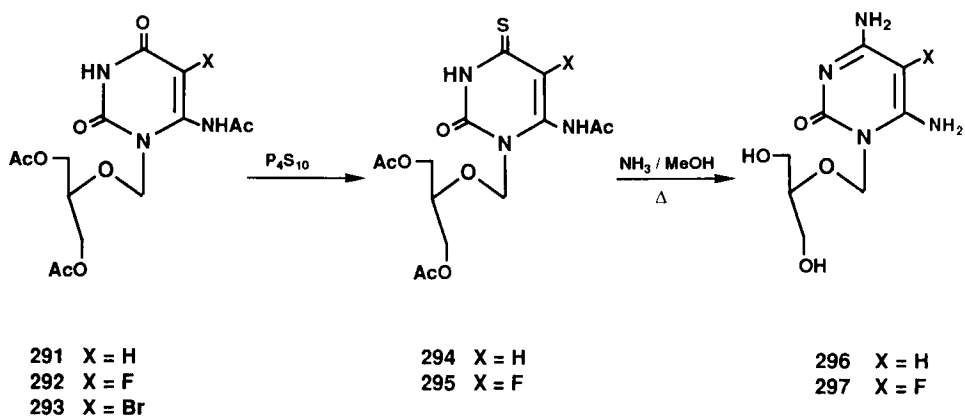


SCHEME 58

SCHEME 59



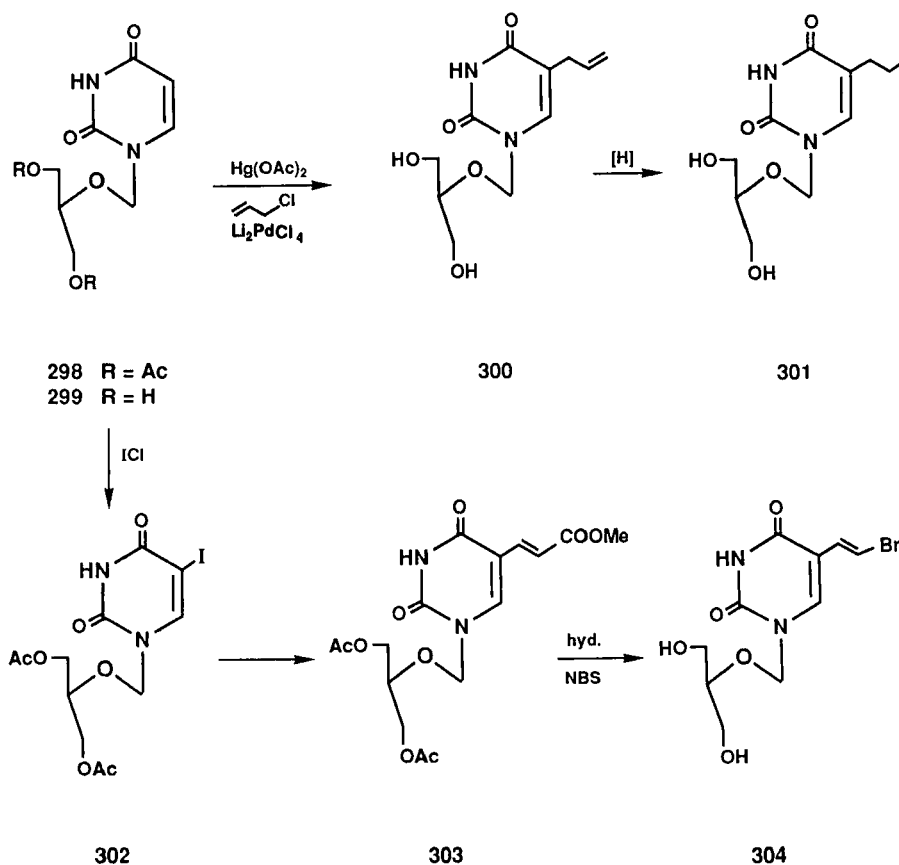
SCHEME 60



SCHEME 61

298 with iodine monochloride led to the 5-iodo derivative **302**. Compound **302** also served as the starting point for the introduction of the bromovinyl side chain at C-5 by the conversion of the 5-iodo to the 5-methyl propenoate **303**. The ester groups in **303** were hydrolyzed, and the bromine atom was introduced using *N*-bromosuccinimide to give **304** (84CJC16). None of the compounds tested showed significant activity.

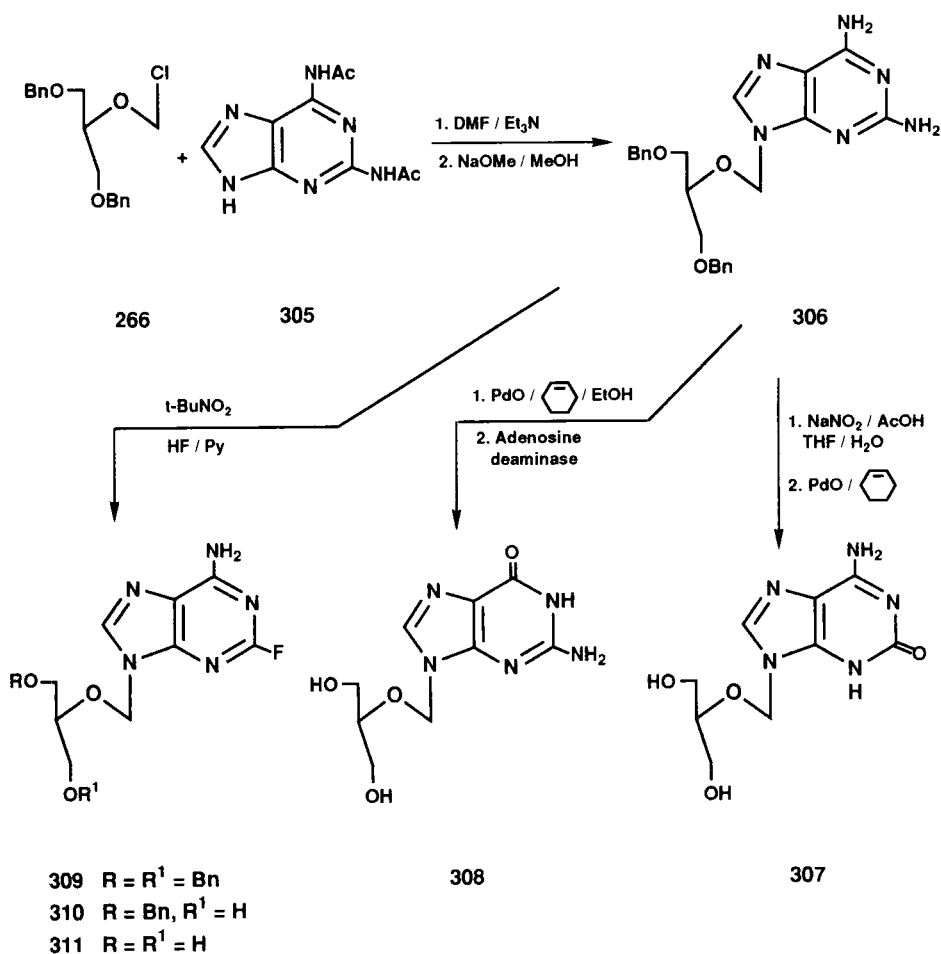
Coupling base **305** with **266** gave **306**. Selective replacement of the amino group by halogens via treatment of **306** with *t*-butyl nitrite in 60% HF/pyridine gave the 2-fluoro derivative. The reaction conditions also resulted in the partial loss of benzyl groups to form **309–311**. The 2-amino group in **306** could also be selectively diazotized to an oxygen function, giving rise to the isoguanine structure. Removal of the benzyl groups gave the



SCHEME 62

isoguanine derivative **307**, which is isomeric with BIOLF-62. The 2,6-diaminopurine derivative was treated with an excess of adenosine deaminase, which was quantitatively converted into BIOLF-62 (**308**) (84CJC241). The dimethylaminomethylene acyclonucleosides were prepared by reactions of the amine group with *N,N*-dimethylformamide dimethyl acetal in DMF/MeOH (85MI5).

The synthesis of the 7-deazapurine and 5-aza-7-deazapurine analogs of DHPG were prepared by the alkylation of the respective heterocycles **312** and **316** with **266** and **267**, respectively. A mixture resulting from the



SCHEME 63

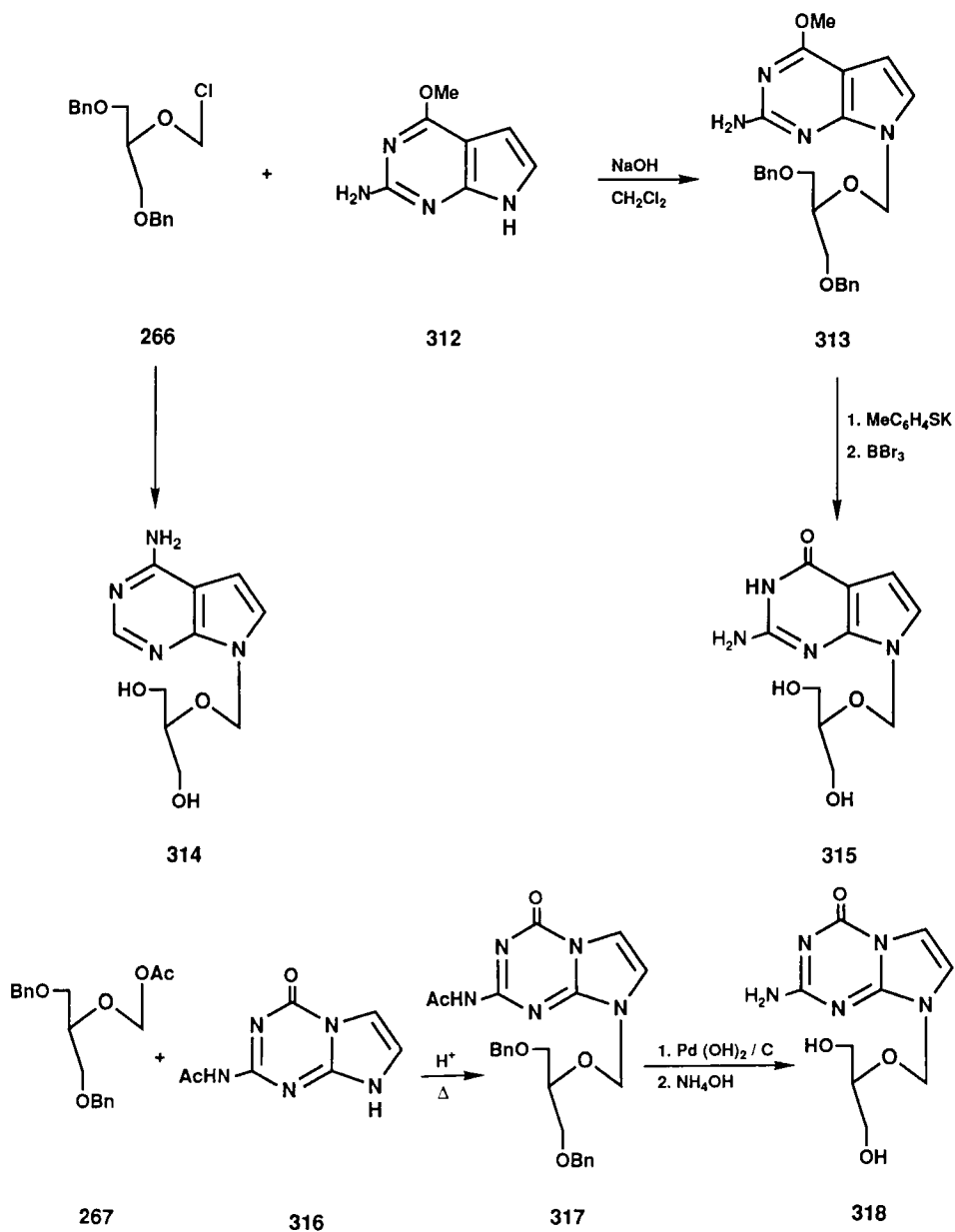
alkylation of N-3 and N-9 was obtained. Deprotection of **313** and **317** gave **315** in the former case, whereas in the latter case the product **318** was contaminated with the dihydro derivative; isolation was done by silylation, purification by chromatography, and then desilylation (85JHC1137). The 4-substituted analogs **314** were prepared via the 4-chloro derivative and then amination (89MI1). Compounds **315** were inactive against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) in cell culture, whereas **318** had moderate antiviral activity. Compound **314** showed poor antiviral activity against Cox B6 virus.

The analogs of tubercidin, toyocamycin, and sangivamycin were prepared by treatment of the sodium salt of 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines with **266**, followed by debromination, and then debenzoylation with BCl_3 . Conventional functional group transformation of the cyano group to CONH_2 , CSNH_2 , and $\text{C}(\text{NOH})\text{NH}_2$ was also done. 4-Chloro-2-methylthiopyrrolo[2,3-*d*]pyrimidine was aminated, desulfurized, and then debenzylated to give the tubercidin analog (89JMC402).

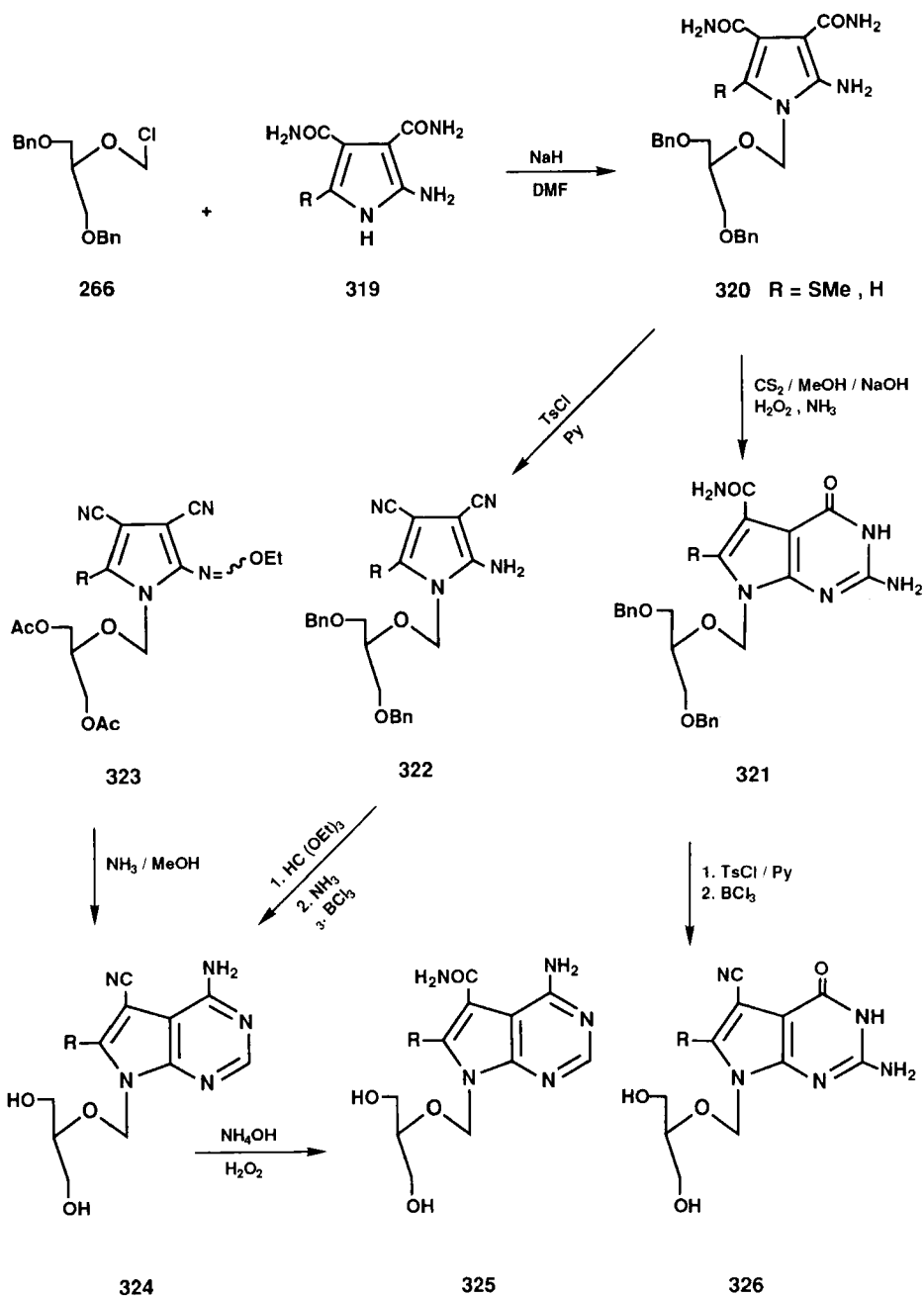
The synthesis of acyclic 7-deazapurine nucleosides involving a pyrrole nucleoside intermediate as a common synthon to both the 7-deazaadenosine and the 7-deazaguanosine analogs was achieved. The construction of these key intermediates (**320**) involves the treatment of the Na salt of the pyrrole derivative **319** with the electrophile **266** in DMF. Desulfurization of **320** ($\text{R} = \text{SMe}$) using Raney nickel afforded **320** ($\text{R} = \text{H}$). Dehydration of the carboxamide functionalities of **320** gave the corresponding dinitrile **322**. Treatment of **320** with carbon disulfide followed by direct oxidation and then treatment with ammonia afforded **321**. The amide was transformed to the nitrile and then deprotected to give **326**. The 7-deazaadenine analogs were prepared by reacting the aminopyrrole **322** with triethyl *ortho*-formate followed by displacement of the ethoxy group by ammonia and subsequent cyclization and deprotection to afford the 7-deazapurine ring system **324**, which could also be prepared from **323**. The nitrile was transformed to the amide **325**. The 7-deazaadenine analogs show activity against HIV (90JMC2162; 92MI7).

The synthesis of 8-azapurine analog **330** was done by the chloroalkylation of the alcohols **265** followed by replacement of chlorine with azide to give **327**. Cyclization with cyanoacetamide gave the 1,2,3-triazoline **328**. Deprotection formed **329**, and cyclization of **328** with ethyl formate and deprotection gave **330** (88S879). The same strategy was used to prepare analogs of types 2.2 and 3.1.

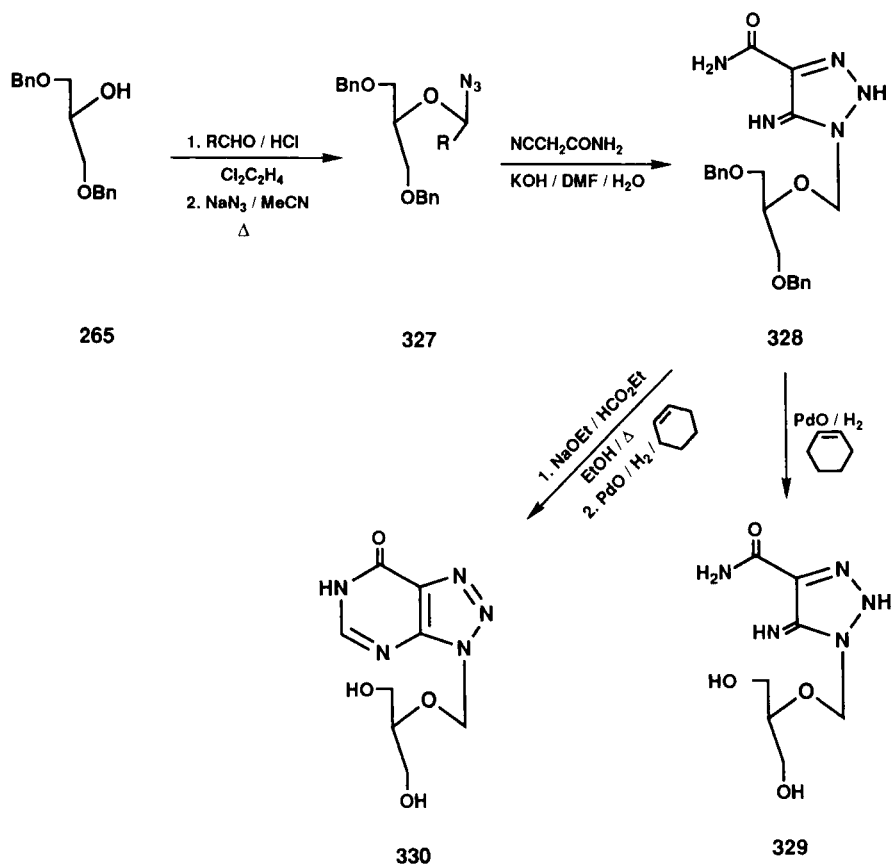
Analog with a sulfur instead of an oxygen atom in the side chain were also prepared. Thus, the starting synthon **332** was prepared from **265** via **331** in four steps. Alkylation of **332** with the silyl derivative of 2-amino-6-chloro-9*H*-purine gave a mixture of **334** and its N-7 isomer that could be



SCHEME 64



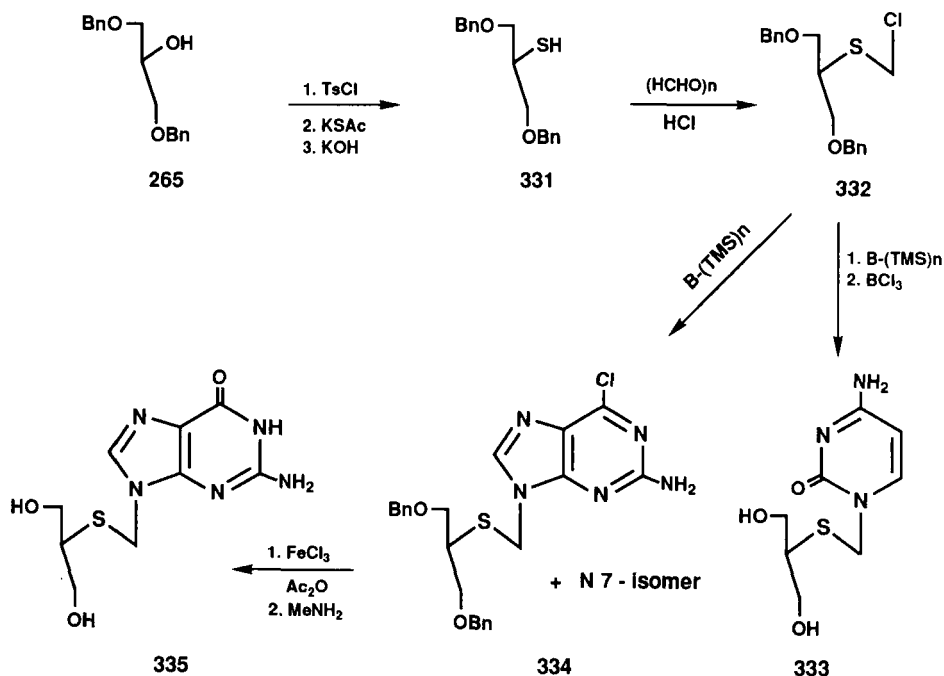
SCHEME 65



SCHEME 66

separated, whereas the use of the respective guanine led to a mixture that could not be isolated. Acetylation of **334** with ferric chloride in Ac_2O and then deacetylation gave **335**. The cytosine analog **333** was similarly prepared from **332** by reaction with a fivefold excess of the cytosine followed by debenzoylation to give **333** (89MI3). Tautomeric purine derivatives were prepared (80USP4199574; 85EUP145207; 90EUP349243). The introduction of an amino group at the 8-position was done by bromination with NBS, hydrazinolysis, and reduction. Guanine analogs were also reported.

The influence of these acyclic nucleosides on the growth of L5178 mouse lymphoma cells and antiherpes activity has been a subject of great interest (83MI1, 83MI2; 84MI2, 84MI3; 85MI3; 90EUP375329, 90USP4968686). The



SCHEME 67

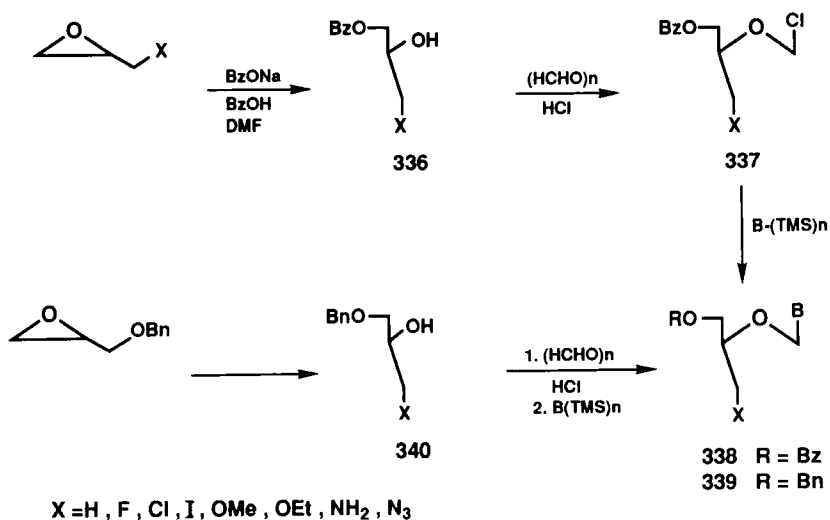
Gu analog (DHPG BIOLF-62) has shown remarkable activity against herpes virus (82CJC3005, 82MI3; 83MI3; 84CJC16; 85EUP161955; 85MI1). *In vitro* studies indicate that DHPG is a potent and broad-acting (herpes simplex virus types 1 and 2, cytomegalovirus, and Epstein-Barr virus) antiherpetic agent. *In vivo* studies indicate its lack of toxicity and its superiority over acyclovir (83JMC759). The 6-H₂-Pu is active against CMV. The 2-amino-6-isopropyl Pu and its esters with long-chain acyl groups were prepared as prodrugs (89AUP388734). The 6-Cl-Gu derivative is active against HSV-1 (84CJC241) and showed high activity against Coxsackievirus 3 in *in vivo* testing in mice. The uracil analogs show little activity against herpes viruses (84CJC16). Pyrimidine analogs inhibited the proliferation of P388 mouse leukemia [88JAP(K)63/060929]. None of the triazine derivatives were active against HSV-1 and HSV-2 or inhibited toxic effects in uninfected HFF cells (93MI1). Antiviral testing showed that a cytosine analog was equivalent to the guanine analog in potency against human cytomegalovirus and Epstein-Barr virus (88JMC144). The structure-activity relations among selected purine and pyrimidine nucleosides have been studied (88AF1545).

The acyclic analogs of tubercidin, toyocamycin, and sangivamycin had only slight-growth inhibitory activity against L₁₂₁₀ murine leukemic cells. The corresponding derivative with CSNH₂ was more potent in inhibiting HCMV but not HSV-1 (89JMC402).

Virucidal activity of an imidazole analog against entero- and coronavirus is increased by the addition of hydroxyalkyl groups in the side chain (88DOK58, 88KFZ833). Neither this analog **333** nor **335** had significant *in vitro* activity against human cytomegalovirus (89MI3).

3. Deoxyhalogeno Analogs

Analogues of DHPG with one of the alcohol functionalities on the side chain replaced by another functionality were also prepared. The chlorodeoxy precursors were prepared from epichlorohydrin by ring opening to give **336**, which chloromethylated to give **337** (X = Cl). Alternatively, ring opening of benzyloxy epoxide gave **340**, whose chloromethylation and coupling gave **339** (86JMC1384; 91MI6). Similarly, the chloro analogs **339** were prepared by reacting bis(trimethylsilyl)adenine and tris(trimethylsilyl)guanine, and bis(trimethylsilyl)uracil after treatment with one equivalent of Bu₄NF, which presumably removes the Me₃Si from their N-9 or O-2, with 1-chloro-3-benzyloxy-2-propoxymethyl chloride and deblocking (89MI6; 90HCA912). Reaction with 2,9-diacetylguanine and then deprotection gave **338** (86JMC1384).



SCHEME 68

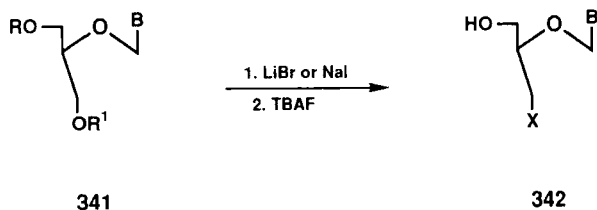
Partial protection of DHPG as bis(monomethoxytrityl) derivative followed by mesylation gave **341**, whose displacement with a variety of nucleophiles and deprotection gave **342** (86JMC1384; 89MI6). An *in vitro* assay against HSV-1 showed that all compounds were less active than DHPG, though the fluoro analog was a good substrate for the viral thymidine kinase.

The optically pure fluoro analogs of thymine and adenine were synthesized (93T713). The (2*S*)-1-fluoro-3-(*R*)-[(4-methylphenyl) sulfinyl]-2-propanol **343** was used as a starting material, which was converted to methoxymethyl ether **344**. Treatment with trifluoroacetic anhydride and 2,4,6-trimethylpyridine in acetonitrile gave, via a Pummerer rearrangement, a geminal trifluoroacetyloxy-tolylthio intermediate as a masked aldehyde, which hydrolyzed *in situ* with mercuric chloride. Reduction with sodium borohydride followed by benzylation gave **345**. Hydrolysis of the methoxymethylene group gave **346**, whose chloromethylation gave **347**. Replacement of the chlorine with thymine gave **348**, which deprotected to **351**. The reaction with 6-chloropurine gave 9-alkylated isomer **349** in addition to a minor amount of N-7 isomer. The major isomer was transformed to the adenine derivative, which deprotected to give **350** (93T713). The synthesis of enantiomerically pure 1',2'-*seco*-nucleosides was almost similarly achieved (92G493).

The dichlorodideoxy derivative **353** was prepared by reacting **352** with trimethylsilylated thymine in presence of *n*-Bu₄NI. Compound **353** was treated with potassium acetate in DMF to give the acetoxy derivative, which was then treated with methanolic ammonia to give **354** in low yield (89MI4).

4. Deoxyazido and Deoxyamino Analogs

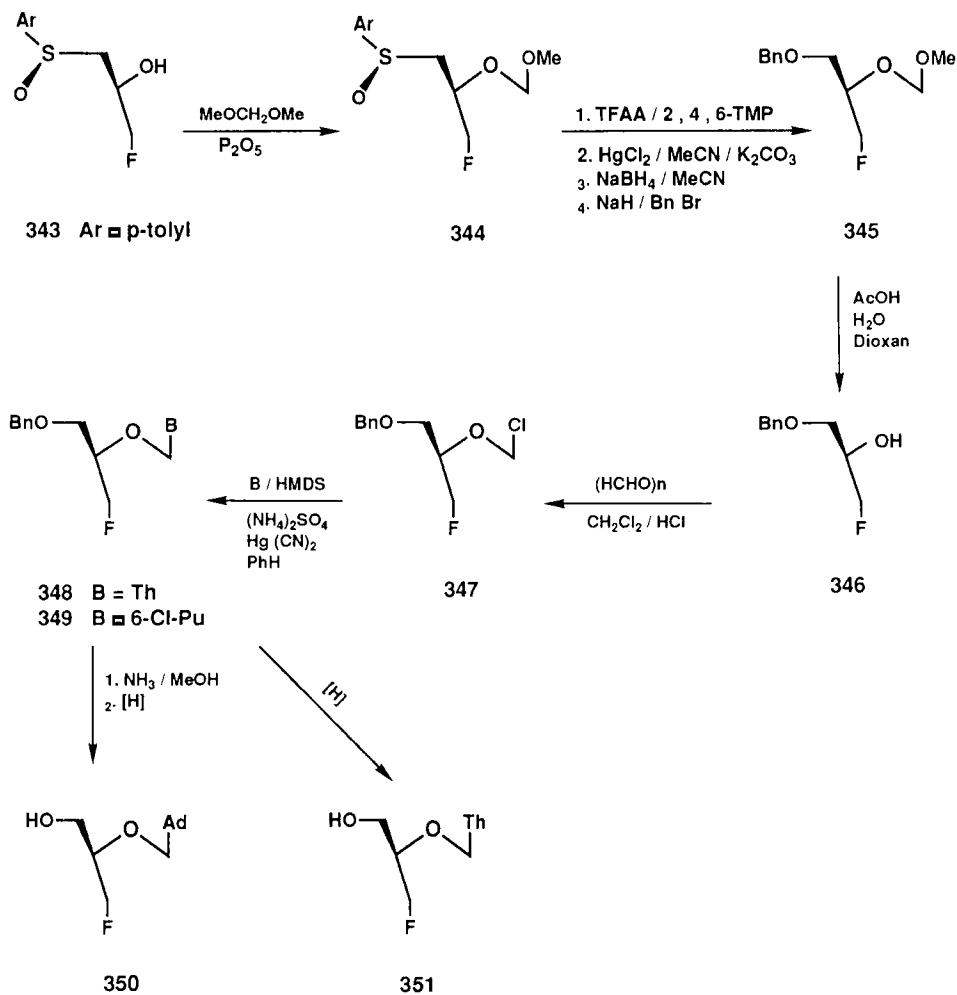
The chiral glycerol derivative **355** was prepared by lipase-catalyzed asymmetric *trans*-esterification. Tosylation of **355** followed by hydrolysis gave **356**. Hydrogenolysis of **356** gave 3-tosyloxy-1,2-propanediol (**357**). After



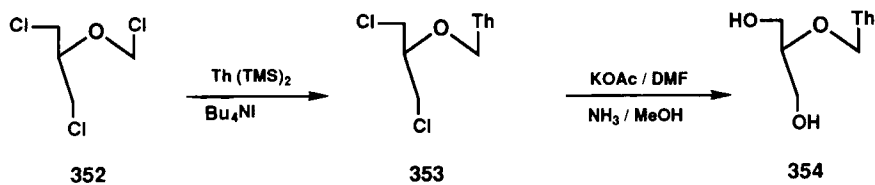
R = DMBS, R¹ = Ms, B = Ad

R = MTr, R¹ = Ts, B = Gu MTr

SCHEME 69



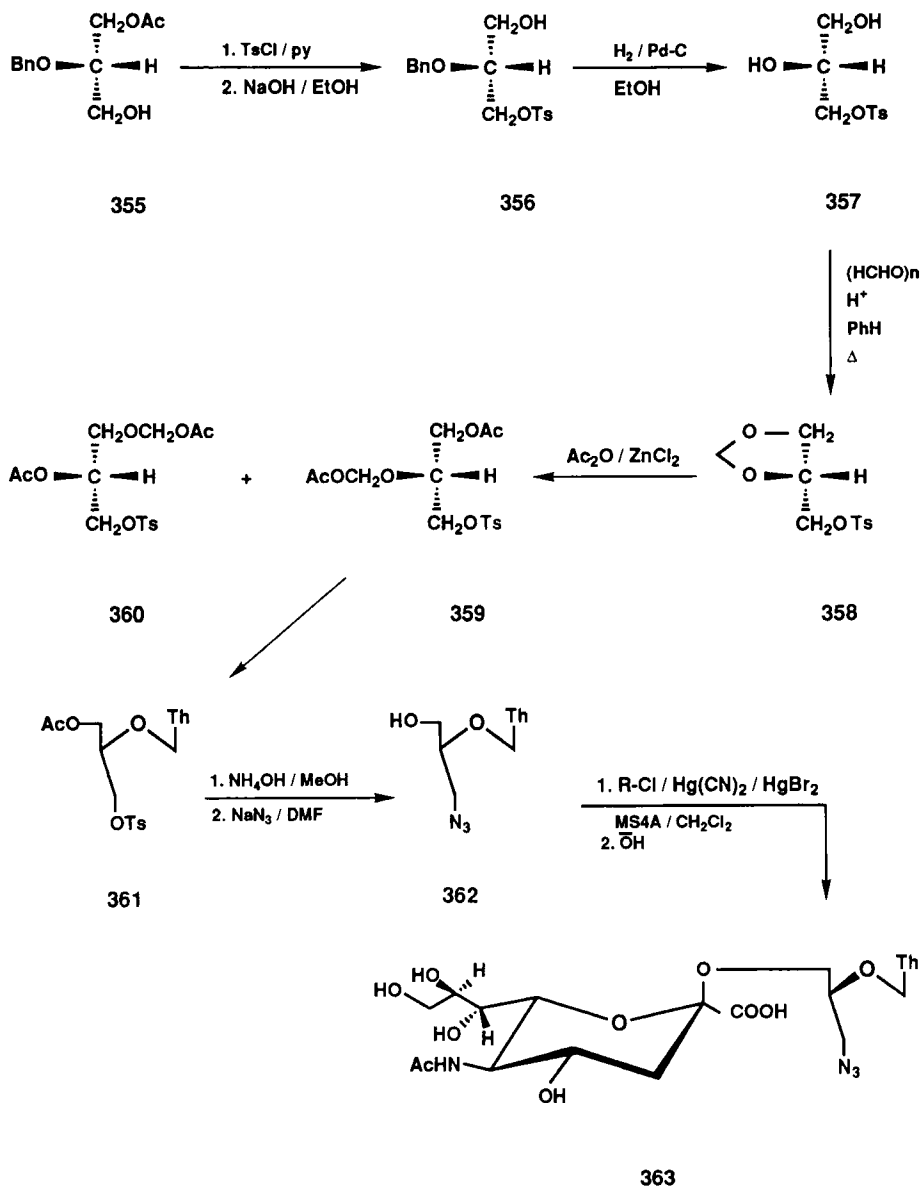
SCHEME 70



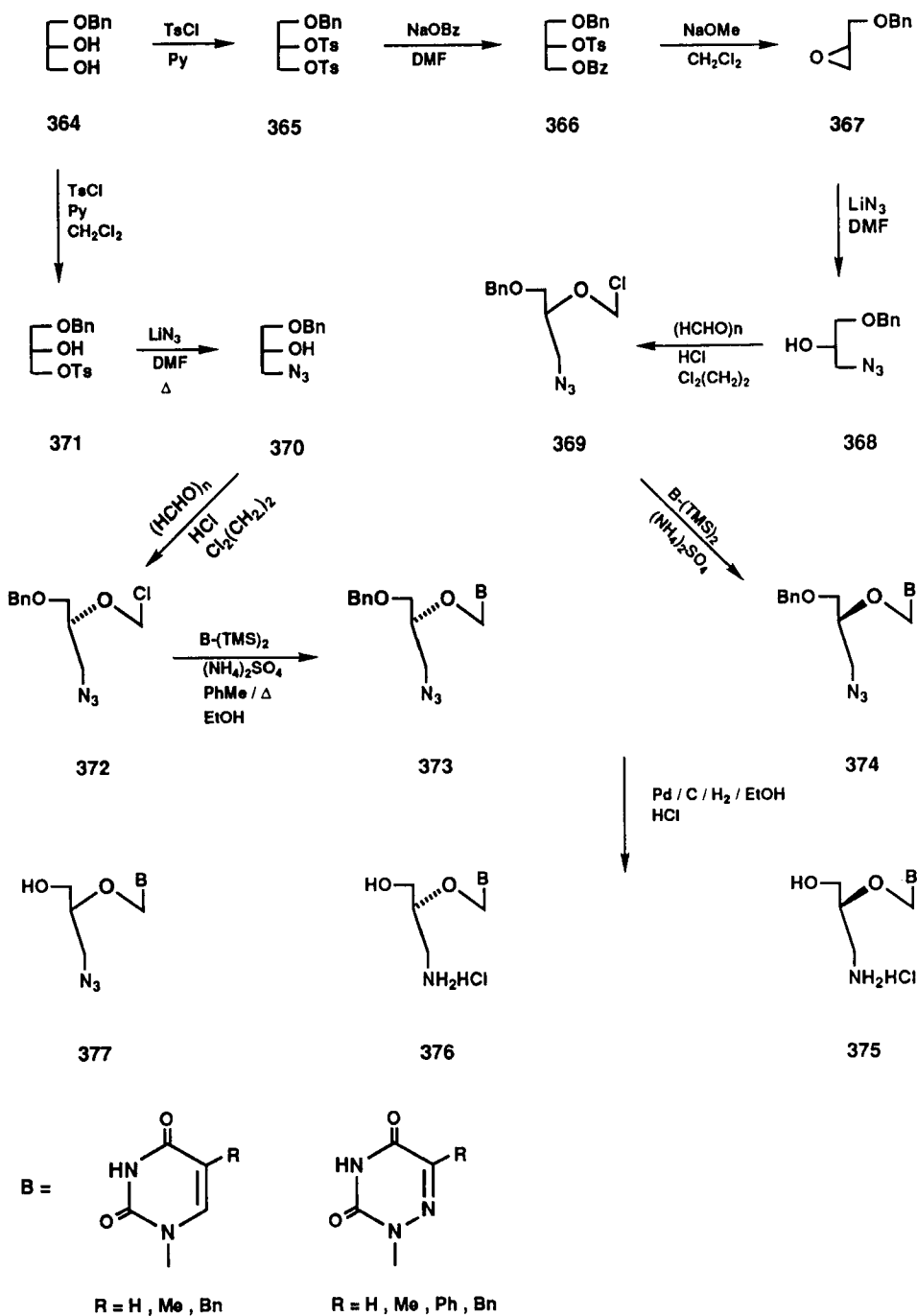
SCHEME 71

formylation of **357** with trioxane, the resulting **358** was acetylated with acetic anhydride and ZnCl_2 to give a mixture of the acetoxymethyl ethers **359** and **360**. The former was treated with bis(trimethylsilyl) thymine in presence of a Lewis acid to give the acyclonucleoside **361**. Acyclo AZT (**362**) was synthesized from **361** by deacetylation followed by treatment with sodium azide in DMF. Treatment of acyclo AZT with the sugar chloride in presence of mercuric cyanide and mercuric bromide gave the respective α - and β -glycosides, whose deacetylation afforded the α - and β -anomers of *N*-acetyl-D-neuraminyl-(2 \rightarrow 2)-(S)-1-[[2-azido-1-(hydroxymethyl)ethoxy]-methyl]thymine (Neu5Ac-acyclo AZT) **363** [90CPB836, 90JAP(K)02/009870].

The optically active compound 1-*O*-benzyl-D-glycerol (**364**), which was prepared from D-mannitol, was used as the common starting material for the synthesis of the key chiral intermediates, (*R*)- and (*S*)-1-benzoyloxy-3-azido-2-propanol (**368**, **370**). Partial tosylation of **364** gave the corresponding 3-*p*-toluenesulfonate **371**, which was further reacted with lithium azide to furnish the (*R*)-azido enantiomer **370**. On the other hand, tosylation of **364** gave the 2,3-di-*O-p*-toluenesulfonate **365**, whose treatment with sodium benzoate in DMF gave the benzoate ester **366**, selectively. Treatment of compound **366** with sodium methoxide resulted in an internal $\text{S}_{\text{N}}2$ displacement reaction, yielding (*R*)-benzyl-2,3-epoxypropyl ether **367** with inversion of configuration at carbon-2. Ring opening of the epoxide **367** with lithium azide afforded the other desired intermediate (*S*)-azido enantiomer **368**. Treatment of the chiral alcohols **368** and **370** with paraformaldehyde and anhydrous hydrogen chloride gas afforded the corresponding chloromethyl ethers **369** and **372**. Each was then coupled with bis(trimethylsilyl)-5-benzyluracil in refluxing toluene under anhydrous conditions to yield the protected azido acyclonucleosides **374** and **373**, respectively. Hydrogenation gave the corresponding amino derivatives. The removal of the benzyl protecting group could not be achieved by the same catalytic hydrogenation conditions. However, by converting the amino derivatives first to their corresponding hydrochloric acid salts, and then following the same reduction conditions just mentioned, the respective final deblocked acyclonucleosides **375** and **376** were obtained. The (*R*) and (*S*) enantiomers have the same affinity for binding to uridine phosphorylase and have marked high water solubility (90MI3). Similarly, thymine, uracil, 6-azathymine, 6-azauracil, 5-phenyl-6-azauracil, or 5-benzyl-6-azauracil were prepared; their debenzylation with boron trichloride in dichloromethane afforded the desired products of azido-acyclic nucleosides **377** (91MI6). None of them exhibited significant antiviral activity against human immunodeficiency virus and herpes simplex virus.

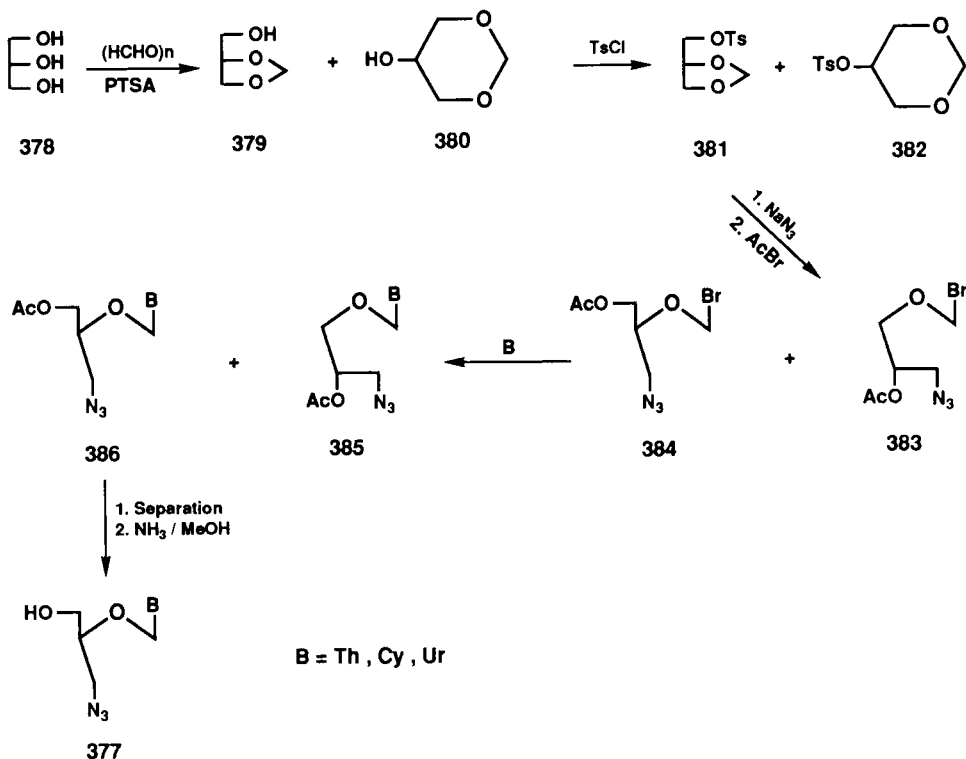


SCHEME 72



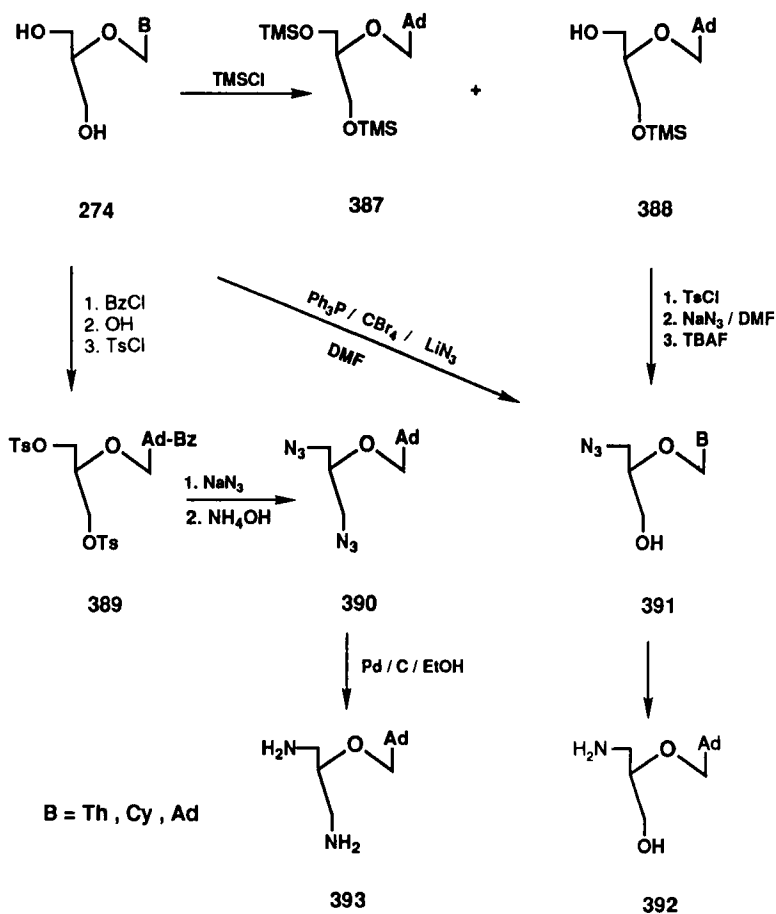
A similar approach utilizing (+)-epichlorohydrin was carried out. Coupling with silylated thymine in the presence of TMSOTf, deprotection, and catalytic hydrogenation gave the amine. *O*-Thexyldimethylsilylation of the azide followed by reduction and then reaction with cyanogen bromide gave the *N*-cyano derivative and with 2,4,5-trichlorophenylformate in DMF containing ethyldiisopropylamine gave the *N*-formyl derivative. Desilylation was done with BU_4NF (91TL1447).

The reaction of glycerol **378** with *para*-formaldehyde catalyzed by *p*-toluenesulfonic acid has been reported to give a mixture of glycerol formal **379** and **380** that upon tosylation and then separation gave two isomers **381** and **382**. Azide salt was reacted with 3-*O*-tosyl derivative **381** to give 3-azidoglycerol formal and treatment with acetyl bromide resulted in acylative cleavage of the C(2) — O bond to give the two isomers bromomethyl ether acetates **383** and **384**. Their coupling with silylated pyrimidines produced a mixture of **385** and **386**, which were separated by chromatography. Deacetylation of **386** gave **377** (89MI7).



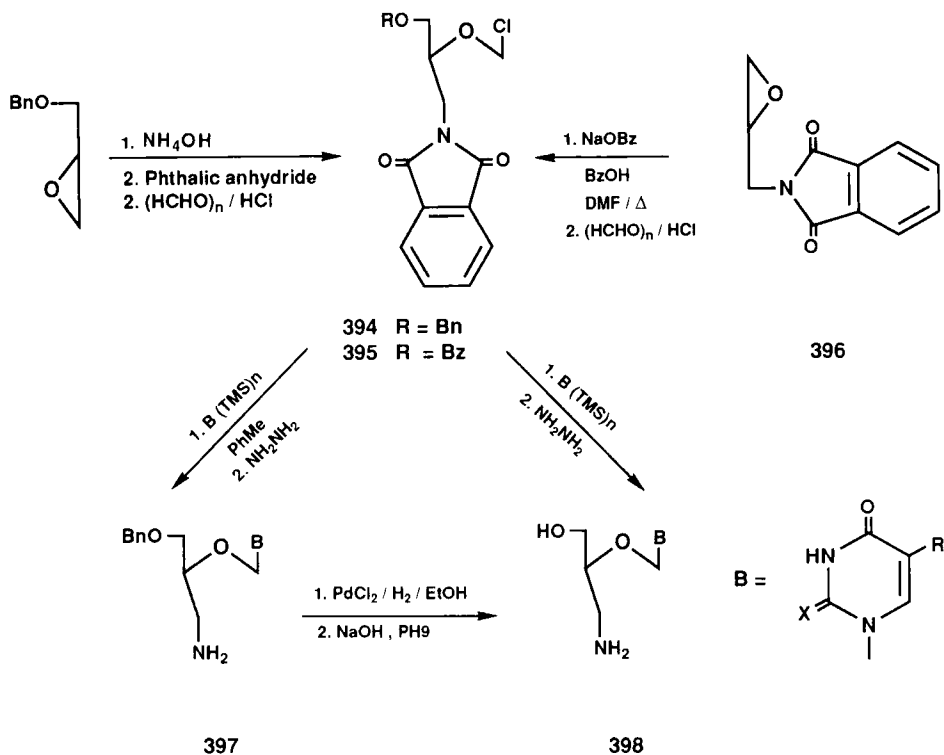
SCHEME 74

Alternatively, the azido functionality was introduced onto an already prepared nucleoside. Thus, silylation of **274** gave **387** and **388**. The hydroxy group in the latter was tosylated, and then displaced with azide ion and deprotected to give **391**, whose reduction gave **392**. The diazide derivative **390** was prepared via the respective ditosylate **389**, whose reduction gave **393** (84CJC241). Treatment of **274** with a combination of triphenylphosphine-carbontetrabromide–lithium azide gave **391**. In the case of an adenine analog, the diazide **390** was found as a by-product (84CJC241). However, the use of carbon tetraiodide led to **391** without by-products [89MI4; 90JAP(K)02/022268]. These compounds have been evaluated for cytotoxicity and inhibition of HIV replication in MT₄, but no activities were detected.



SCHEME 75

The introduction of an amino function into the acyclic sugar moiety started with the treatment of 3-benzyloxypropylene oxide with concentrated aqueous ammonium hydroxide, which then underwent S_N2 substitution to give 1-amino-3-benzyloxy-2-propanol. Further reaction with phthalic anhydride in toluene resulted in the formation of *N*-(3-benzyloxy-2-hydroxypropyl)phthalimide. Chloromethylation by reaction with *para*-formaldehyde and dry HCl in 1,2-dichloroethane yielded (1-benzyloxy-3-phthalimido-2-propoxy)methyl chloride (**394**). Alternatively, reaction of epichlorohydrin with potassium phthalimide gave **396**. It was converted with sodium benzoate in the presence of benzoic acid in DMF, and then treated with 1,3,5-trioxane in presence of HCl to **395**. With **394** and **395**, the persilylated bases were alkylated, and the phthaloyl protecting group was removed with hydrazine in ethanol to form **397** from **394** and **398** from **395**. Deprotection by cyclohexene in ethanol with a catalytic amount of $Pd(OH)_2$ afforded **398** (91MI5). Most showed little toxicity toward HeLa cells and 50% inhibitory levels against HSV-1 (90HCA912).



SCHEME 76

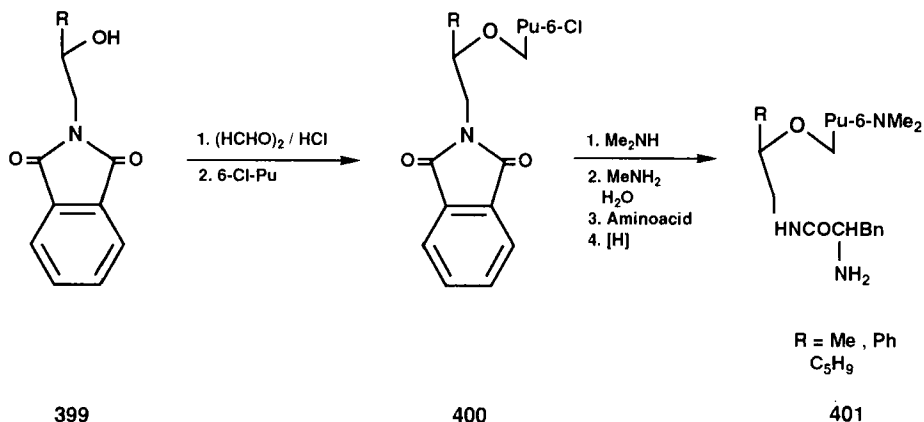
The aminodeoxy analogs were found to be very potent inhibitors of uridine phosphorylase isolated from sarcoma, and they exhibited no apparent cytotoxicity against sarcoma 180 host cells. Furthermore, they have shown excellent water solubility, which is a factor critical for the formulation that often limits the usefulness of a particular compound as a chemotherapeutic agent (85JMC971).

Similarly, the puromycin analogs were prepared from **399** by chloromethylation and coupling with 6-chloropurine to give **400**, which was reacted with dimethylamine, followed by dephthaloylation, coupling with DL-*N*-carbobenzoxypheylalanine, and then hydrogenolysis to give **401** (85JPS1302).

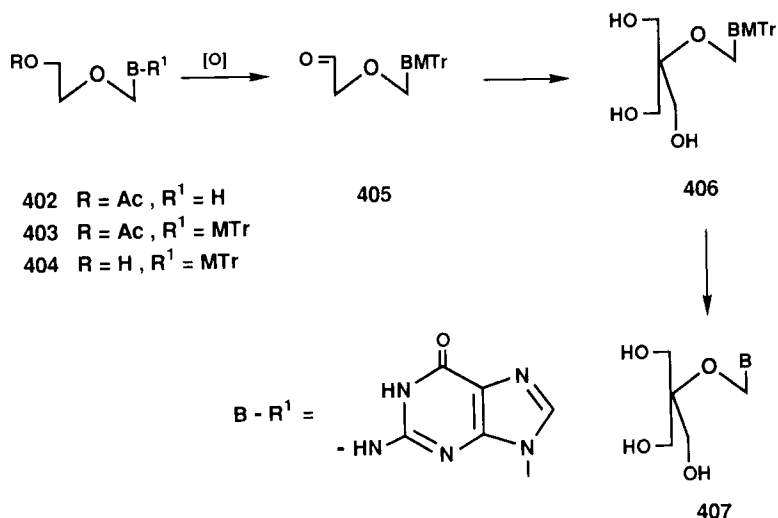
5. Branched-Chain Analogs

The trihydroxy analog **407** was prepared by acetylation of acyclovir to give **402**, which monomethoxytritylated to **403** and then deacetylated to **404**. Moffatt oxidation of **404** gave **405**, which upon a crossed aldol-Cannizaro reaction gave **406**, whose deprotection gave **407** (86JMC1384).

The starting material, 1,3-dibenzoyloxy-2-propanol **265**, is easily oxidized to the ketone **408** using *N*-chlorosuccinimide and dimethyl sulfide. Compound **408** was smoothly converted into the epoxide **409**. The epoxide ring was opened by the attack of benzylate anion at the least hindered site to produce 2-benzoyloxymethyl-1,3-dibenzoyloxy-2-propanol (**410**), which was activated as the thiomethyl ether system **411** using acetic anhydride in DMSO. The thiomethyl ether is readily activated by iodine, allowing nucleophilic attack at the methylene position. As a result, compound **411** was

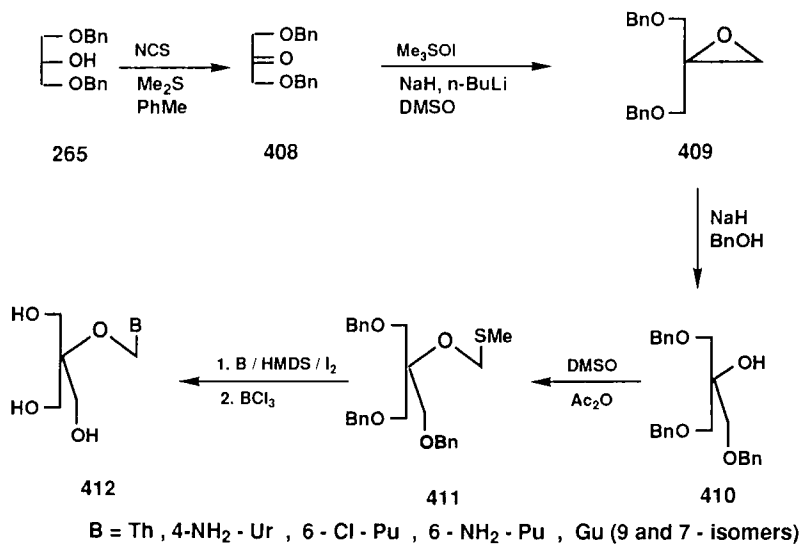


SCHEME 77

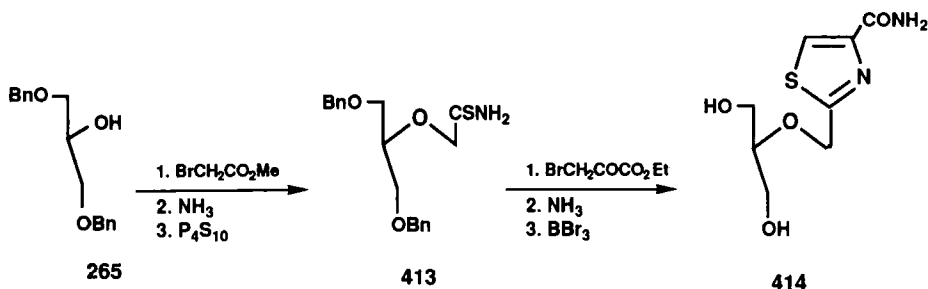


SCHEME 78

coupled to purines and pyrimidines using the silylated base procedure. As usual, the guanine derivative was produced in the lowest yield. The N-7 isomer is produced in significant quantity along with the N-9 isomer. The N-7 isomer crystallizes from solution after removal of the *N*-acetyl group



SCHEME 79



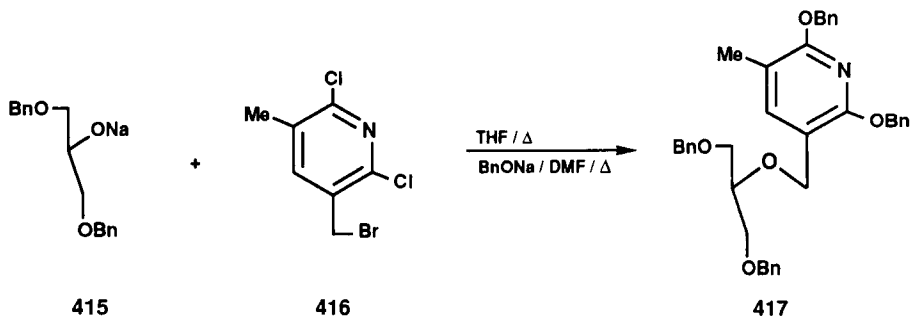
SCHEME 80

from the direct condensation product. The route chosen to the adenine derivative involved 6-chloropurine in the condensation step. Very little of the N-7 isomer is present at the end of the reaction. The chlorine at position 6 is readily displaced by ammonia to give the adenine derivative (84CJC1622; 87BBA127). Only the guanine derivative had an ED-50 of less than 100 $\mu\text{g/ml}$ with HSV-1.

6. Acyclo-C-nucleoside Analogs

The C-nucleoside analogs of this type of acyclonucleosides were prepared by essentially two methods: sequential *O*-alkylation of **265** with methyl bromoacetate followed by amidation; and sulfurization to give **413**, which cyclized with ethyl bromopyruvate to the thiazole carboxylate, whose amidation and debenzilylation gave thiazofurin analog **414** (87H947).

Alternatively, heterocycles carrying a bromomethyl group could be used as alkylating agents to provide the targeted acyclo-C-nucleoside analogs. Thus, alkylation of the sodium salt **415** with **416** followed by substitution of the chlorine atoms gave **417** (91T10065).

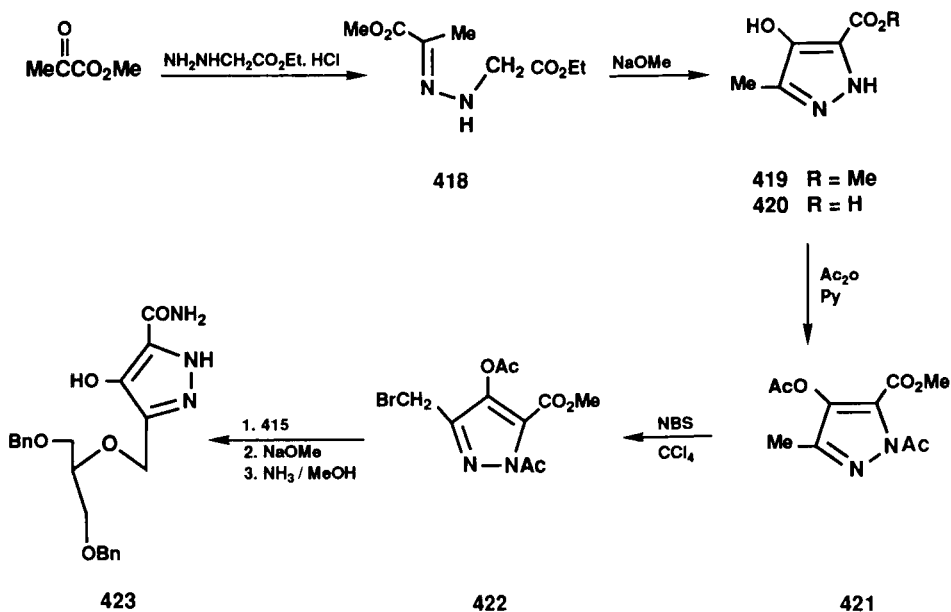


SCHEME 81

The acyclic analog of pyrazofurin that possesses the side chain of ganciclovir was prepared by constructing the heterocyclic ring, prepared from the hydrazone of methyl pyruvate **418**, by heating with the sodium alkoxide in THF to give **419** and **420**, followed by esterification and acetylation to **421**. Its bromination gave **422**, which, upon reaction with **415** and then deprotection, gave **423**, which has no antiviral activity (91MI4).

7. Carboacyclic Analogs

The carbo analog (Penciclovir) **431** of DHPG was prepared starting from diethyl malonate (**424**). Upon alkylation **424** gave **425**, which was reduced and benzylated to **426**. The latter was converted to **427** in four steps and then reacted with the sodium salt of guanosine, followed by debenzylation by a phase transfer catalysis to give **431** (84MI4). A shorter route to the carbo analog of DHPG **431** was carried out starting with triester **429**. Its reduction gave the triol, which upon partial protection gave **428**, followed by the conversion of the unprotected hydroxy group to a bromine to give **430** (85TL4265). Alkylation of 2-amino-6-chloropurine with the bromodeoxy derivative **430** gave the 9-isomer, whereas the 7-isomer was barely detect-



SCHEME 82

able. Acid hydrolysis of the 9-isomer converted the 6-chloro to the 6-oxo function and removed the acetonide group to give **431** (87JMC1636), which showed the highest activity against herpes simplex virus type 1 and to a lesser extent type 2. In some tests it is more active than acyclovir (87JMC1636; 92MI1). The dihexanoate ester is the most active ester (84MI4; 87JMC1636). The same strategy was used to prepare C-substituted analogs starting with substituted ethyl bromoacetates [88JCS(P1)2757].

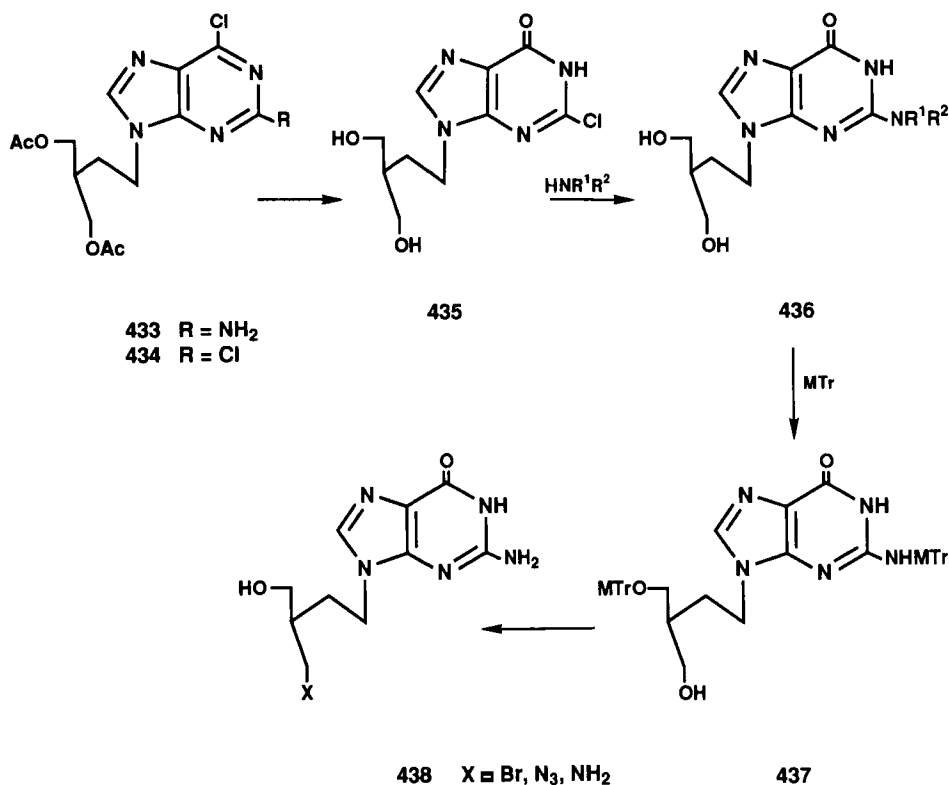
Tosylation of the isobutyridene analog of **428** followed by reaction with iodine and coupling with the sodium salt of guanine and then deprotection gave **431** (86JMC1384).

Alkylation of the thymine with bromide **427** presents a problem. The best condition to introduce the alkyl group onto N-1 is to use excess thymine and K_2CO_3 in DMF- H_2O , whereby the product was obtained in addition to the N-3 mono- and N-1, N-3 dialkylated derivatives, as well as monobenzylated derivatives. Debenzylation gave **432** ($X = OH$), whose reaction with $Ph_3P/CBr_4/LiN_3$ gave **432** ($X = N_3$) in low yield as a racemate (92MI5).

The crystal and molecular structures of 9-[4-hydroxy-3-(hydroxymethyl)-butyl]guanine (BRL39123; Penciclovir) and its prodrug 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-aminopurine (BRL42810, Famciclovir) were reported (90MI2).

The 2,6-dichloropurine analog **434** was prepared in two ways, either by alkylation of the base with 2-acetoxymethyl-4-iodobutylacetate to give **434** and its 7-isomer, or by chlorination of **433**. Hydrolysis of **434** gave **435**, in which the chlorine could be substituted with amines to give **436** [89JCS(P1)2207]. The 2-amino-6-iodopurine may also be used as a base in the coupling (90EUP352953). The respective 2-*N*-hydroxyguanine showed potent antiherpes virus activity in a cell culture test [89JCS(P1)2207]. Functional group conversion of one hydroxyl group of **436** was achieved via the bis(monomethoxytrityl) derivative **437** by bromination and deprotection to **438** ($X = Br$). Its conversion to the azide followed by reduction gave the amine whose formylation gave the formyl derivative, which showed moderate antiherpes virus activity, whereas **438** ($X = N_3$) showed only weak activity [88JCS(P1)2777].

The corresponding ethers proceeded from diol **439**. Selective acetylation of **439** and then methylation gave **441** ($R = H$). In contrast, selective allylation of **439** followed by hydroxylation gave **440**. Periodate oxidation and reduction gave the corresponding alcohol, whose acetylation gave **441**. Debenzylation by catalytic hydrogen transfer or hydrazinolysis followed by bromination gave **442**; subsequent alkylation of the base and then deprotection gave **443** [88JCS(P1)2777]. A weak antiherpes virus activity was observed for **443** ($R^1 = CH_2OH$).

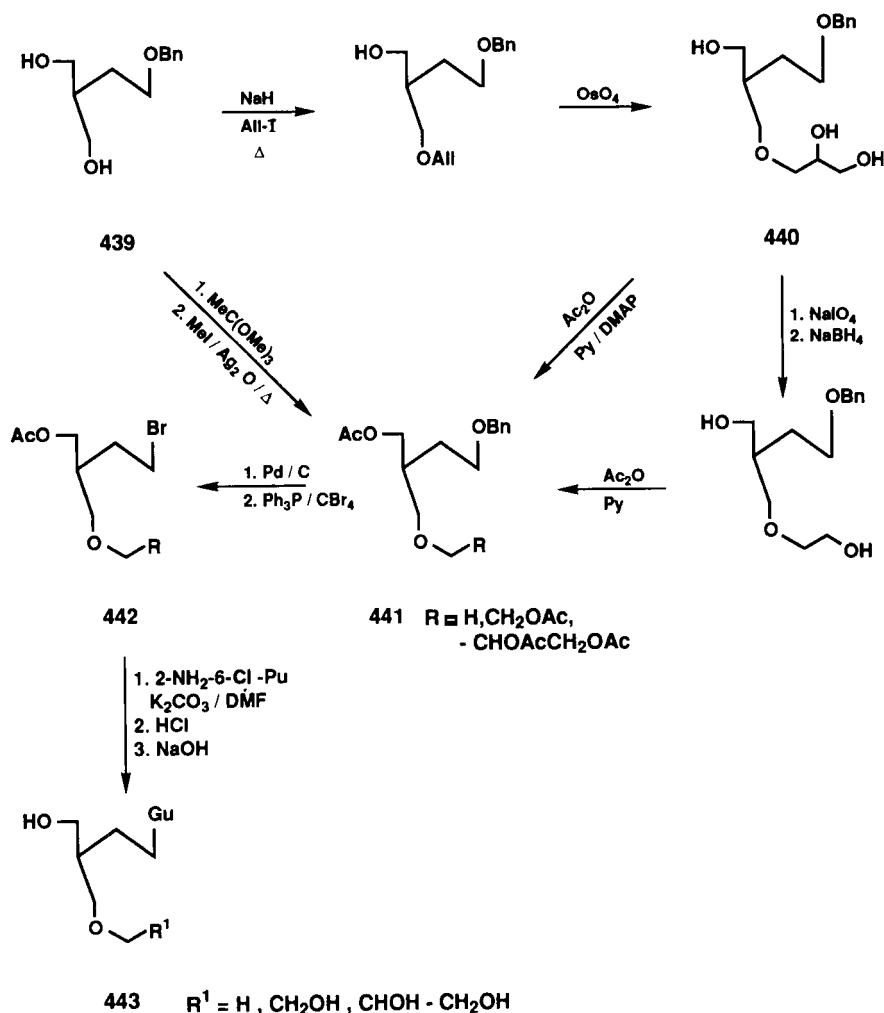


SCHEME 84

by reduction of the ester group to give the alcohol that upon attempted tosylation gave the chloro derivative **445**. Coupling of either adenine or the guanine precursor 2-amino-6-chloropurine with **445** formed the nucleosides **446**, whose debenzoylation gave **447**. In the case of a guanine precursor, further treatment with alkali was required to obtain the guanine analog, which exhibited significant antiviral activity against HSV-2 (87JMC943).

The preparation of 2,2-bis(hydroxymethyl)cyclopropyl analogs **450** and **452** was accomplished starting with the cyclopropane derivatives **448**, which, when reduced, benzoylated, ozonized, reduced, and then tosylated, gave **449**. Coupling of the latter with adenine and then debenzoylation gave **450**, whereas coupling with 2-amino-6-chloropurine gave **451** followed by acid hydrolysis to give the guanosine **452** (88JMC2304).

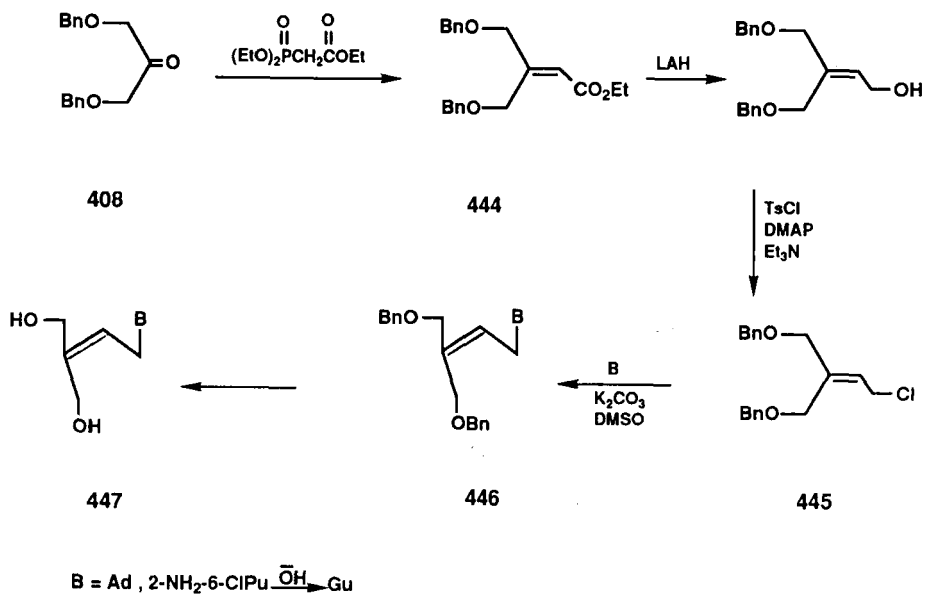
The branched-chain analogs were prepared as shown previously for the nonbranched ones from triester **429**. Alkylation of its anion with iodometh-



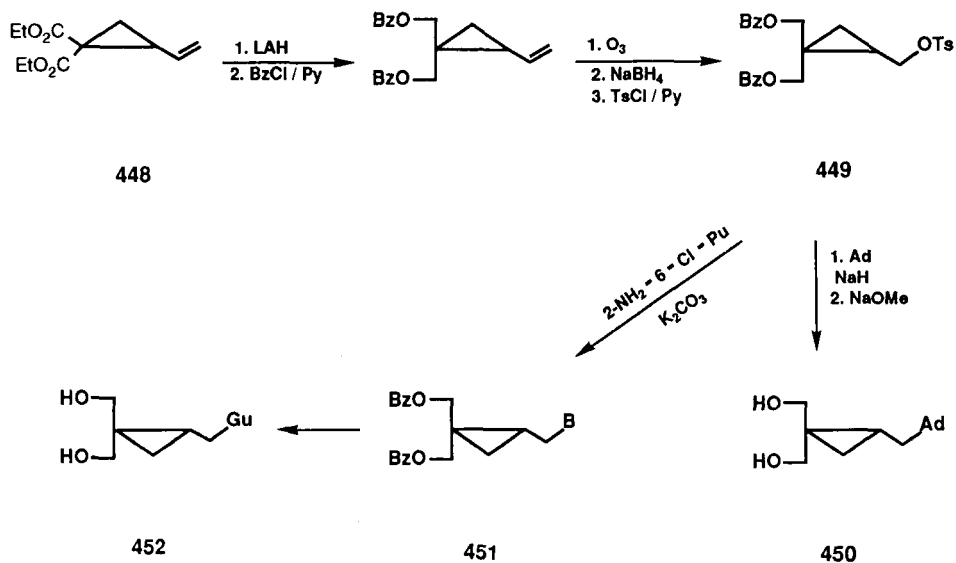
SCHEME 85

ane or benzyl chloromethyl ether gave **453**, followed by reduction with sodium borohydride or LiAlH_4 to give the respective triol. Acetonation of the triol was accomplished with little selectivity, whereby **454a** was formed in appreciable quantities in addition to **454b**. Bromination of the latter gave **455**. Coupling of **455** with 2-amino-6-chloropurine gave **456**, whose hydrolysis gave the guanosine analog **457** [88JCS(P1)2767].

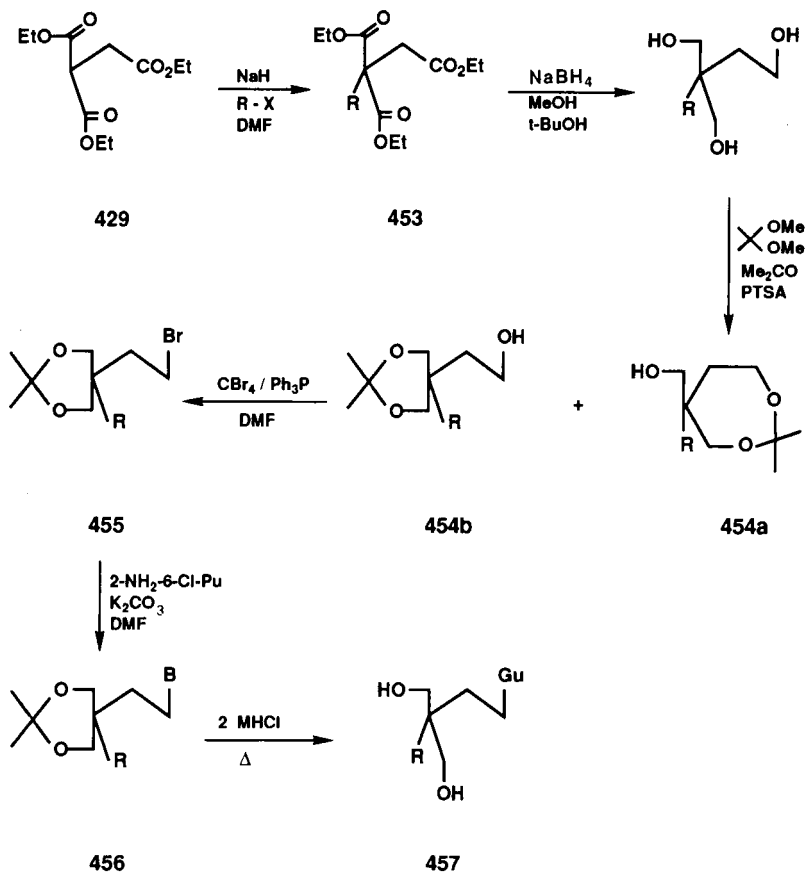
The fluoro analog **463** was prepared from diethyl acetoxyacetaldehyde **458** by alkylation of its anion with benzyl-2-bromoalkyl ether to give **459**, whose



SCHEME 86



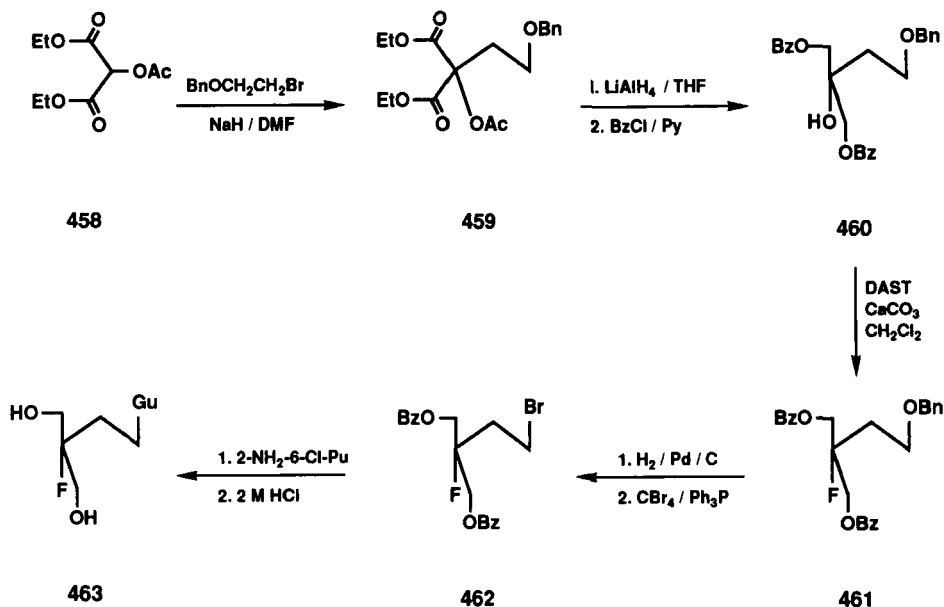
SCHEME 87



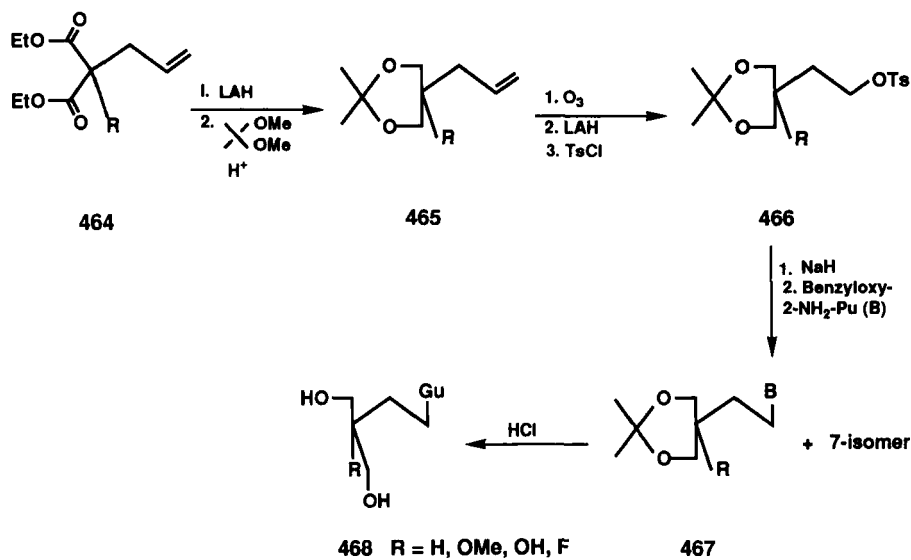
SCHEME 88

reduction followed by benzoylation gave **460**. Fluorination of **460** gave **461**. Debenzylation followed by bromination gave **462**, which was used in the alkylation of 2-amino-6-chloropurine followed by acidic hydrolysis to give **463** [88JCS(P1)2767].

An alternative route to the carba-ganciclovir and its modified side chain was started by the malonate derivatives **464**, where the allyl group serves as a masked 2-hydroxyethyl function. Thus, reduction of **464** gave the respective diol that was protected as the isopropylidene **465**, which upon ozonolysis, reduction, and tosylation gave **466**. The respective tosylates were used in the alkylation of 2-amino-6-benzoyloxypurine to give **467**, in addition to the 7-isomeric product. Hydrolysis gave the carba-ganciclovir analog **468** (89JHC1261). Their antiviral activities were evaluated.



SCHEME 89

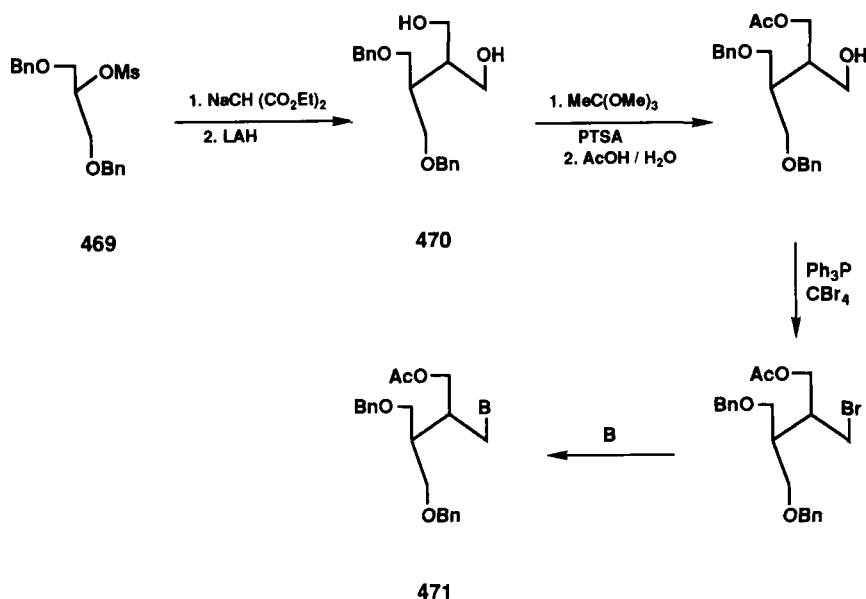


SCHEME 90

The alcohol **470** was prepared from the mesylate **469** by reaction with diethyl malonate followed by reduction to give **470**, whose selective acetylation was carried out by reaction with trimethyl orthoacetate followed by acid hydrolysis of the cyclic orthoester intermediate. Bromination and then coupling gave **471** [88JCS(P1)2757].

The analogs **479** and **480** were prepared from the *O*-protected glycoaldehyde diethylacetals **472** by a *trans*-acetalization to **473**, which was chlorinated to **474** and then reacted with diethyl malonate followed by reduction to give **475** or **476**. Cyclohexylidenation and then debenzoylation of **475** gave **481**. Benzoylation of **476** gave **477**, which upon debenzoylation, tritylation, and then fluorination gave **478**. Detritylation of the last gave the respective alcohols. The alcohols from **478** and **481** were converted to the bromides and/or the mesylates. Alkylation of 2-amino-6-chloropurine with these bromides or mesylates gave **479** and **480**, which were converted to the racemic 9-substituted guanines [88JCS(P1)2757].

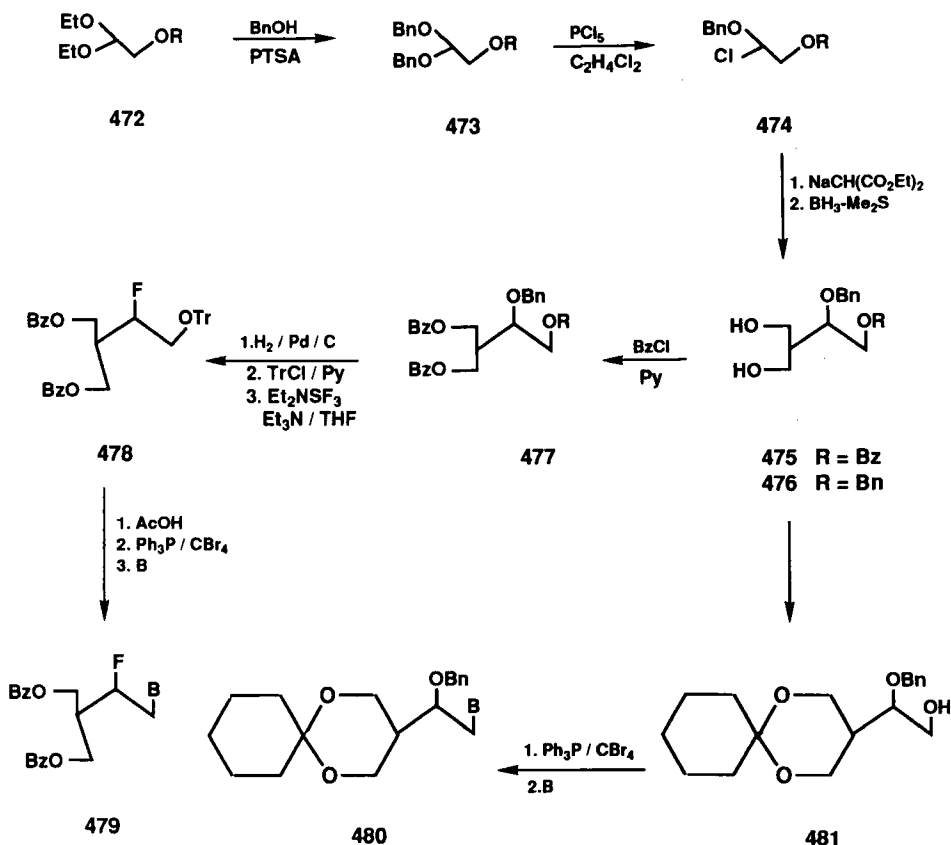
Synthesis of the 1'-methoxy derivative **484** commenced with the alkylation of the anion of diethyl malonate with a suitable bromoacetal, followed by reduction to give **482**, which upon acetylation and then reaction with acetyl chloride and thionyl chloride gave the α -chloroether **483**. Reaction of **483** with the trimethylsilylated 2-*N*-acetylguanine using tin (IV) chloride



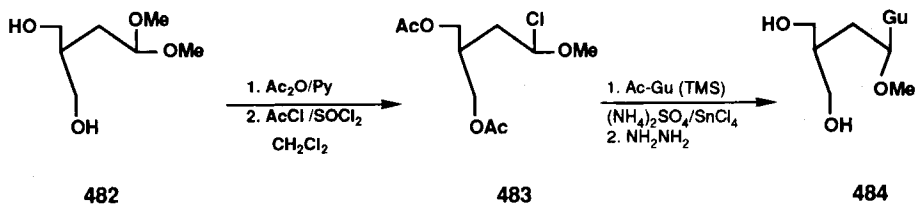
SCHEME 91

as a catalyst gave a mixture of 9- and 7-alkylation products, whose deacetylation gave **484** and its isomeric product, respectively [88JCS(P1)2767]. All of these acyclonucleosides with branched chains were tested for antiviral activity in cell cultures. The most active was the 3'-fluoro, but it had only about one-third of the activity of the lead compound 9-(4-hydroxy-3-hydroxymethylbutyl)guanine against herpes viruses.

This type of acyclic nucleoside could be prepared by a Michael addition process. Thus, when 2-amino-6-chloropurine was reacted with **485**, and 8:1 mixture of the N-9 (**486**) and N-7 cyclopropylpurines was produced. When the chloroethylidene malonate was used, the ratio became 40:1. Catalytic hydrogenation of **486** in presence of base effected both dehalogenation and 1,2-cyclopropane bond fission to provide **487**. Its reduction and acetylation gave Famciclovir **488** (91EUP420559; 92TL4609).



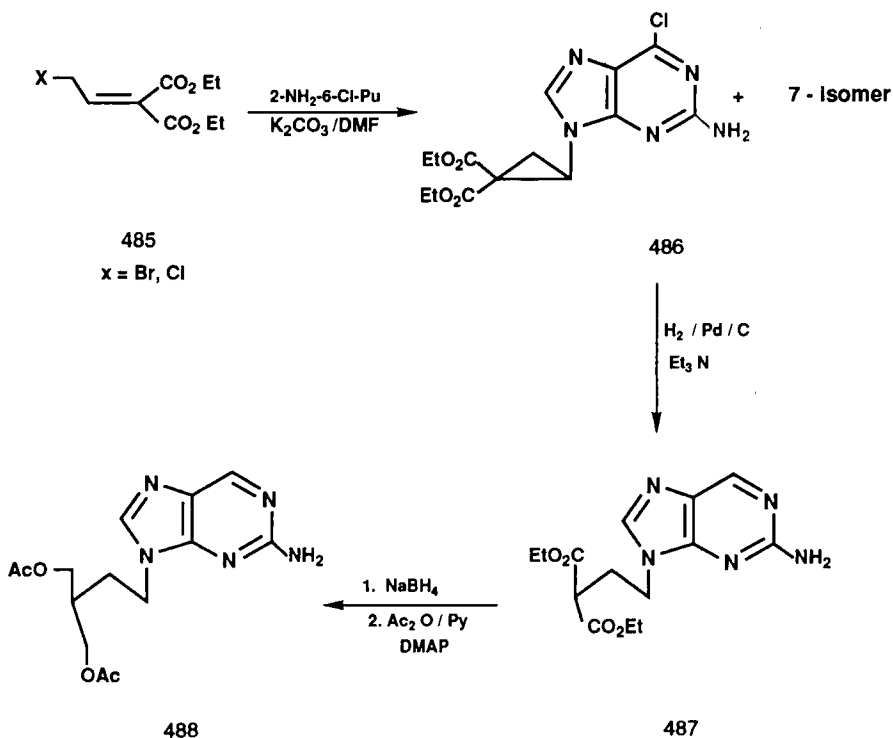
SCHEME 92



SCHEME 93

9. Carboacyclic Analogs via Heterocyclic Ring Construction

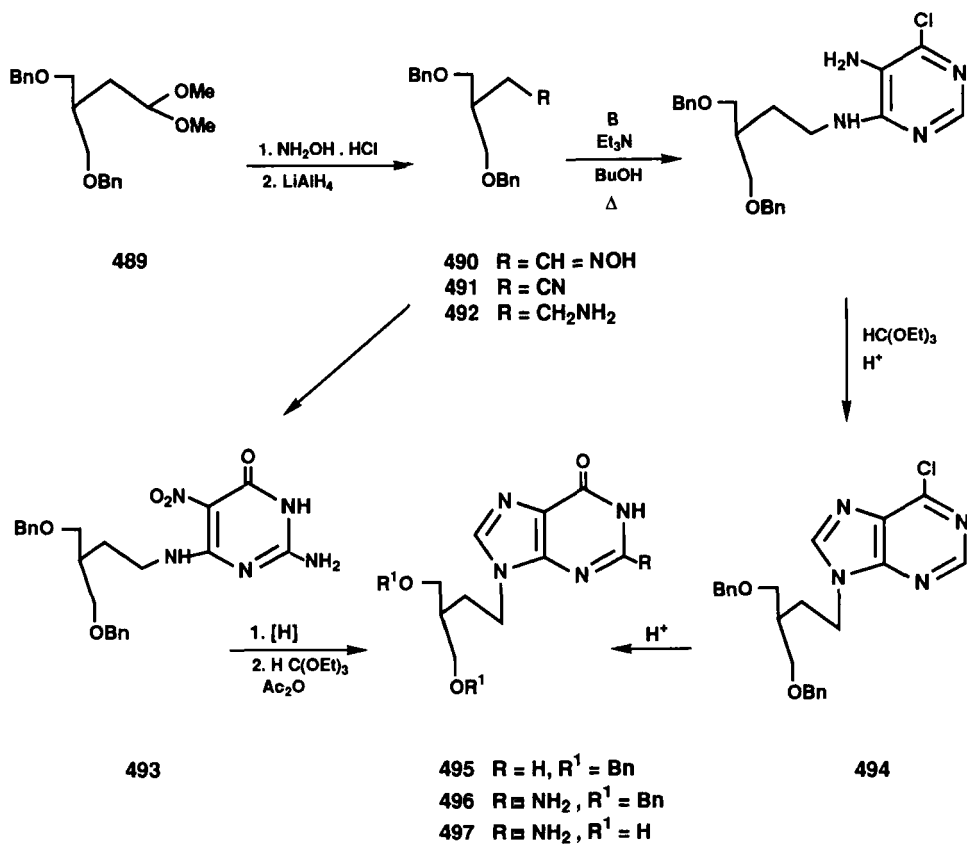
The synthesis of the carboacyclic analogs may be performed by constructing the heterocyclic ring on a suitable functionalized side chain. Thus, the acetal **489** was synthesized in a similar manner to **426**. Its reaction with hydroxylamine hydrochloride gave a mixture of the oxime **490** and nitrile



SCHEME 94

491, which upon reduction gave **492**. Reaction of **492** with 5-amino-4,6-dichloropyrimidine followed by cyclization with ethyl orthoformate gave **494**, which upon hydrolysis gave the hypoxanthine analogs **495**; its amination, however, gave the adenine analogs (72SC345). The respective guanine analog **496** was prepared by cyclization of **493**. Debenzylation of **496** gave **497**. The crystal and molecular structure of Penciclovir (BRL 39123) and Famciclovir (BRL 42810) were determined. In the former, the plane of the acyclic N-9 substituent is orthogonal to the purine ring. It has an extensive network of intermolecular hydrogen bonds. In Famciclovir, however, there are no major hydrogen bonding interactions, but there are π - π interactions between parallel overlapping pyrimidine moieties (90MI2).

The pyrimidine ring in **499** could be constructed by the condensation of **492** with acrylamide **498**, followed by base-catalyzed cyclization to **499**



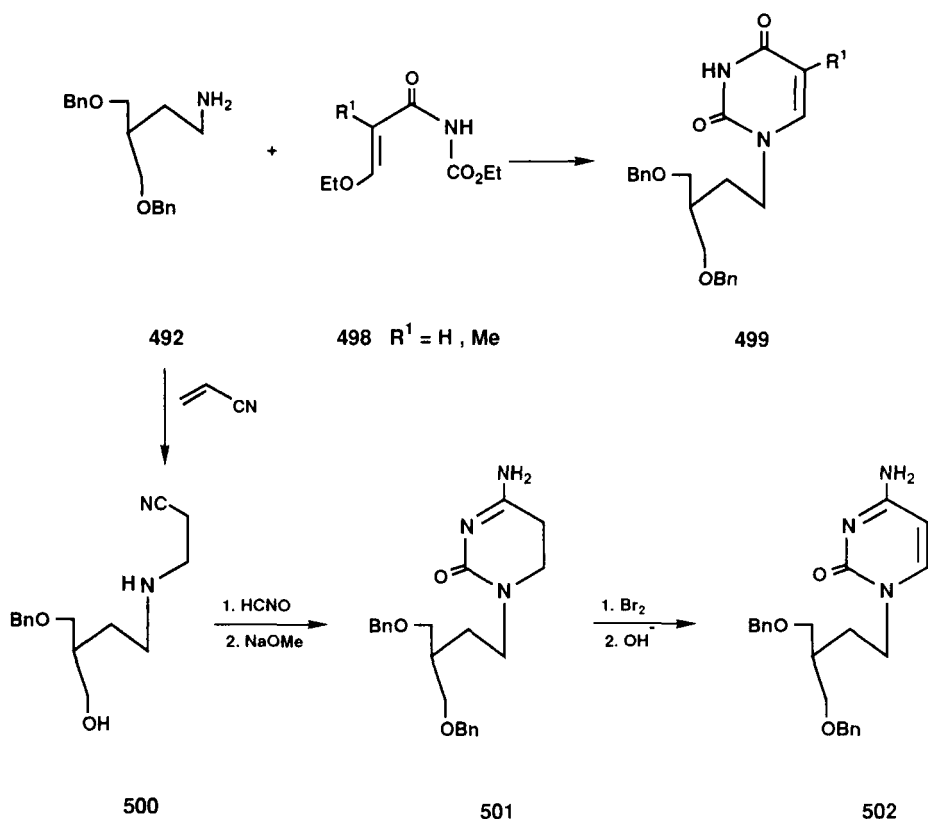
SCHEME 95

(72SC345). Cyanoethylation of **492** gave **500**, whose cyclization gave **501**, which upon bromination and dehydrobromination gave **502** (72SC345).

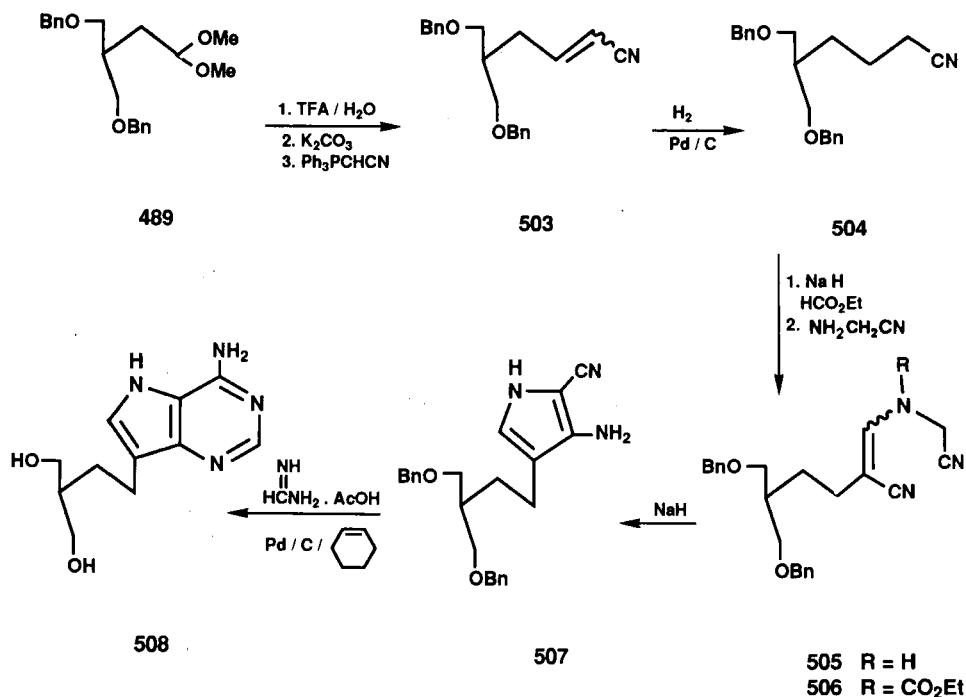
10. Carboacyclic C-Nucleoside Analogs

The carboacyclic C-nucleosides could be constructed from **489** by cyano-methylation to give **503**, which upon reduction gave **504**. Iminoolefination of **504** gave **505**, whose reaction with ethyl chloroformate gave **506**, which was cyclized to the pyrrole **507**; the pyrimidine ring then was formed to give **508** [91JCS(P1)195].

A series of conformationally restricted acyclic pyrimidine nucleosides fixing the base-sugar orientation in the anticonformation by forming a carbon bridge between them has been prepared. This was based on the

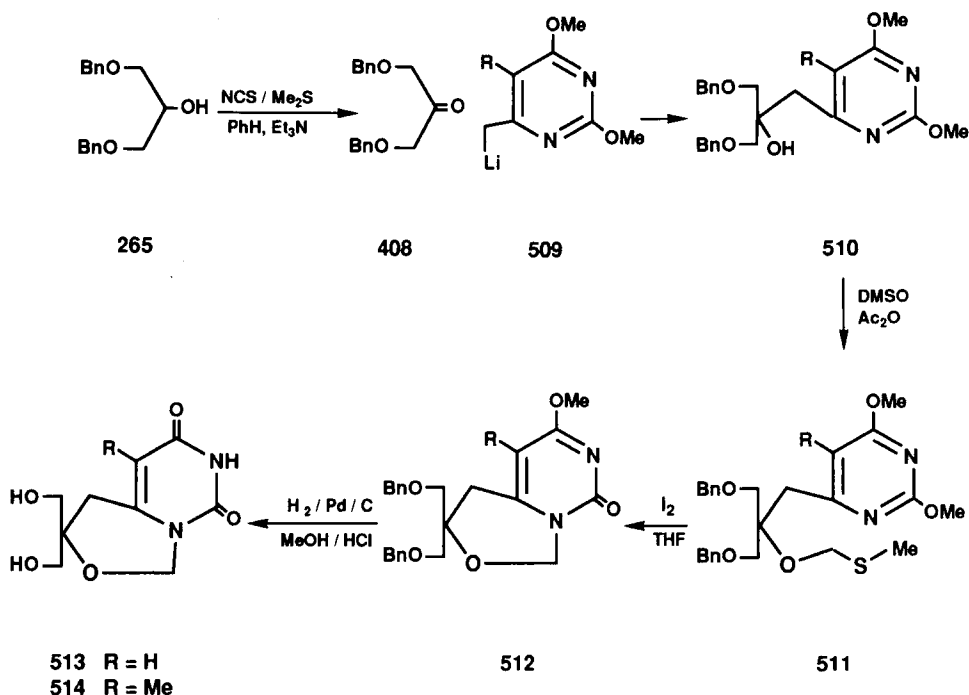


SCHEME 96



SCHEME 97

hypothesis that if the nucleoside is to be a good substrate for HSV-TK and be active against herpes viruses, it must exist in the anti conformation rather than the syn conformation. Thus, the C-6 side chain was connected via an addition reaction of the lithiated 6-methyl pyrimidine derivatives **509** with 1,3-bis(benzyloxy)-2-propanone **408** to give **510**. The lithio derivatives were prepared from the pyrimidine bases with LDA in tetrahydrofuran. The tertiary hydroxyl group of the side-chain group was smoothly converted to **511** on treatment with a mixture of acetic anhydride and anhydrous dimethyl sulfoxide. Ring closure of **511** to bicyclic **512** was accomplished with iodine in dry tetrahydrofuran. An initial electrophilic activation of the sulfur atom of the (methylthio)methyl group by the iodine took place to generate a reactive sulfonium species, which promoted the nucleophilic attack at the methylene position by the nitrogen of the pyrimidine ring. Deprotection of **512** gave **513** or **514**, whereas the cytidine derivative was obtained by debenzoylation with boron trichloride, followed by a displacement of the methoxy group using saturated methanolic ammonia (92JOC3354).



SCHEME 98

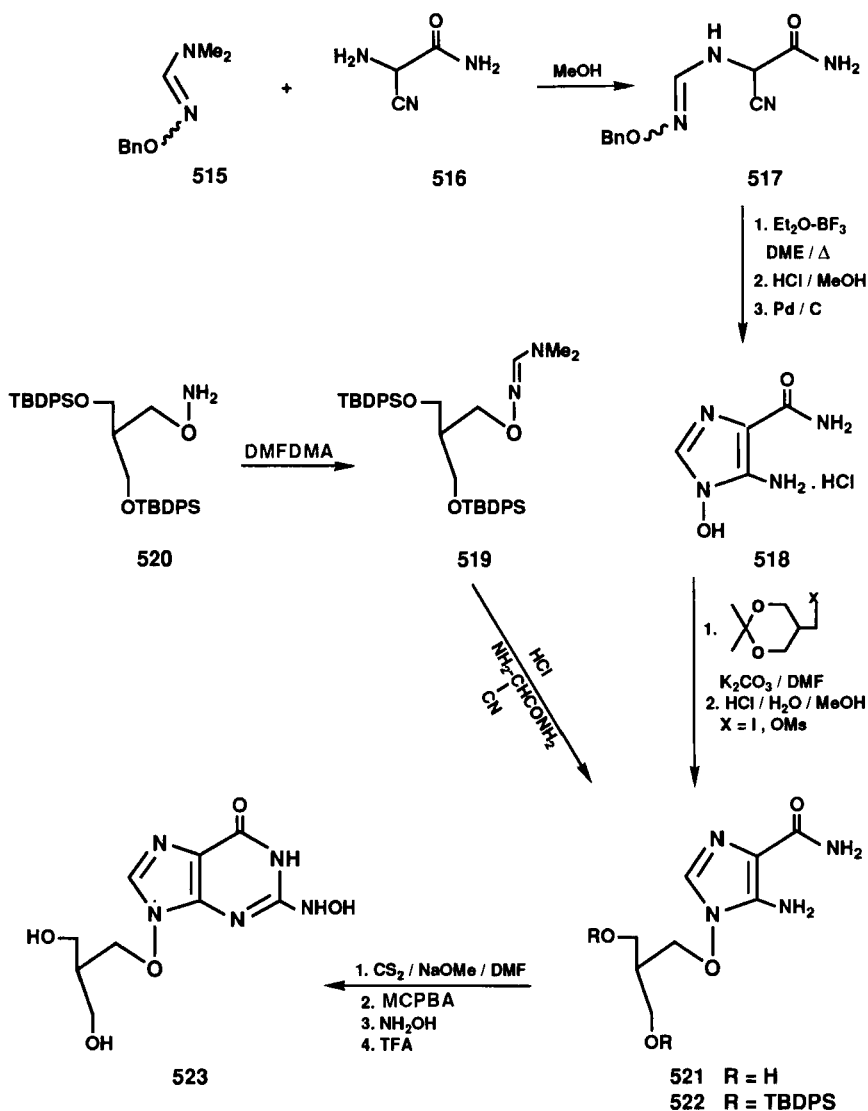
11. Translocation of Oxygen with Carbon and Aza Analogs

Analogues with a translocated atom of the ether linkage by a carbon atom have been also prepared. Thus, reaction of 2-amino-2-cyanoacetamide hydrochloride **516** with *N,N*-dimethyl-*N'*-benzyloxymethanimidamide **515** in methanol gave **517** as an unstable intermediate. Cyclization of **517** with the Lewis acid diethylether–boron trifluoride in 1,2-dimethoxyethane followed by catalytic hydrogenolysis over 10% palladium on charcoal afforded **518**, isolated as its hydrochloride. Its alkylation with the 5-iodomethyl-2,2-dimethyl-1,3-dioxane, in the presence of potassium carbonate, gave the 1-alkoxyimidazole. A similar yield was obtained by using the mesylate and catalytic amounts of lithium iodide. Deprotection under acidic conditions gave the imidazol-1-ylxyalcohols **521** (90S893).

Alternatively, the construction of these nucleosides was achieved from the alkoxyamine derivative **520** by conversion to the respective formamidine **519**. Transamidination followed by boron-trifluoride-catalyzed cyclization gave the imidazoles **522**. Their cyclization was effected using sodium methyl-

xanthate to give the purine thiolates, which upon oxidation with MCPBA gave the sulfonate, which directly reacted with hydroxylamine. Deprotection gave **523** [89JCS(P1)2207].

The alkoxyamine **524** was converted to the urea derivative **525**, whose cyclization with 3,3-dimethyloxypionate or ethyl-3,3-diethoxy-2-methyl-

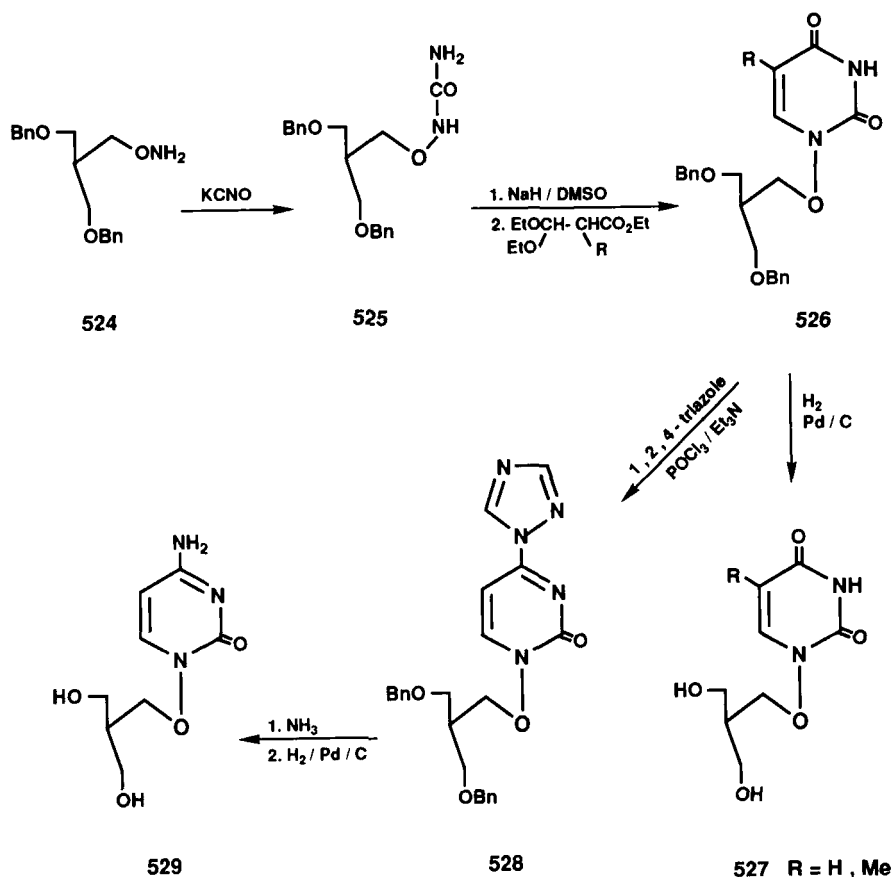


SCHEME 99

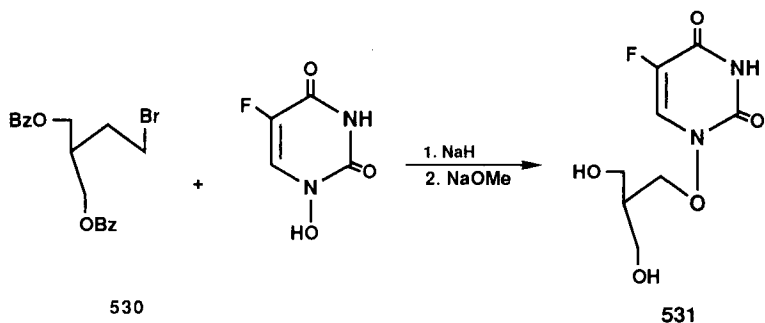
propionate was effected to give the pyrimidine derivatives **526**. Their catalytic hydrogenation gave **527** (88TL4013). The cytosine derivative **529** was prepared via the triazolo derivatives **528**, which upon aminolysis and deprotection gave **529**. None of these compounds had significant antiviral activity.

The 5-fluoro analog **531** was prepared by alkylation of 5-fluoro-1-hydroxyuracil, via initial formation of its dianion with the appropriately functionalized halide **530** and then conventional deprotection [90JCS(P1)2175]. No significant activity was noted against herpes simplex virus type 1 and 2, varicella zoster, cytomegalovirus, or Epstein-Barr virus.

Replacement of the oxygen by nitrogen in the preceding analogues led to the 9-alkylaminoguanines **536**. They were prepared from the 9-aminogua-

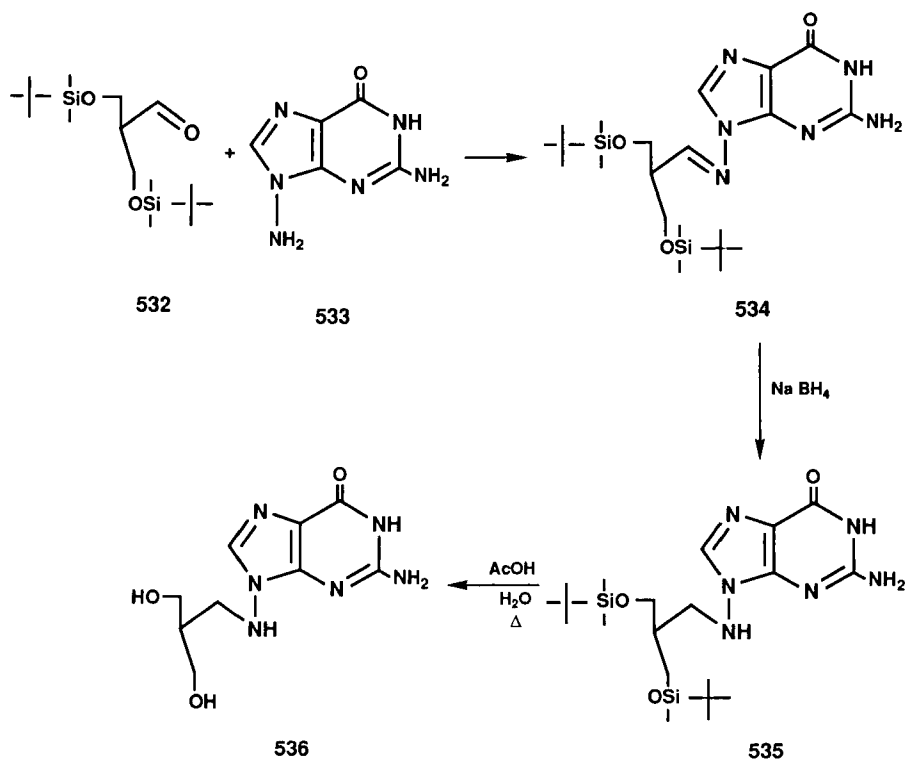


SCHEME 100



SCHEME 101

nine **533**, by condensing it with aldehyde **532** to give **534**. Reduction of **534** gave **535**, which was followed by desilylation to give **536** (88TL5995). They are selective antiherpes virus agents, although less potent than analogous 9-alkyl and 9-alkoxyguanines.



SCHEME 102

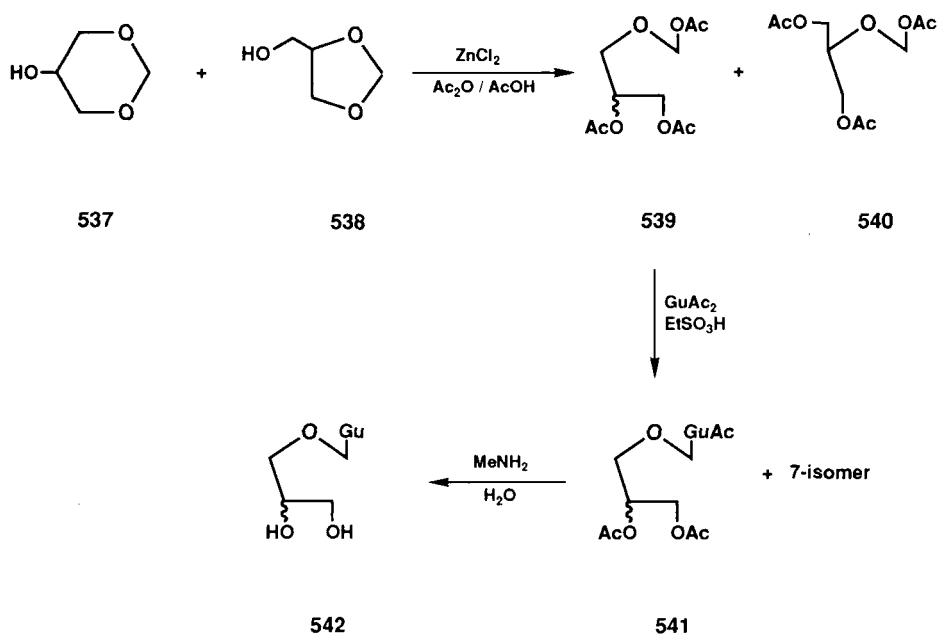
B. 1',2'- AND 4',5'-*diseco*-NUCLEOSIDES (TYPE 2.2)

1. General Methods of Construction

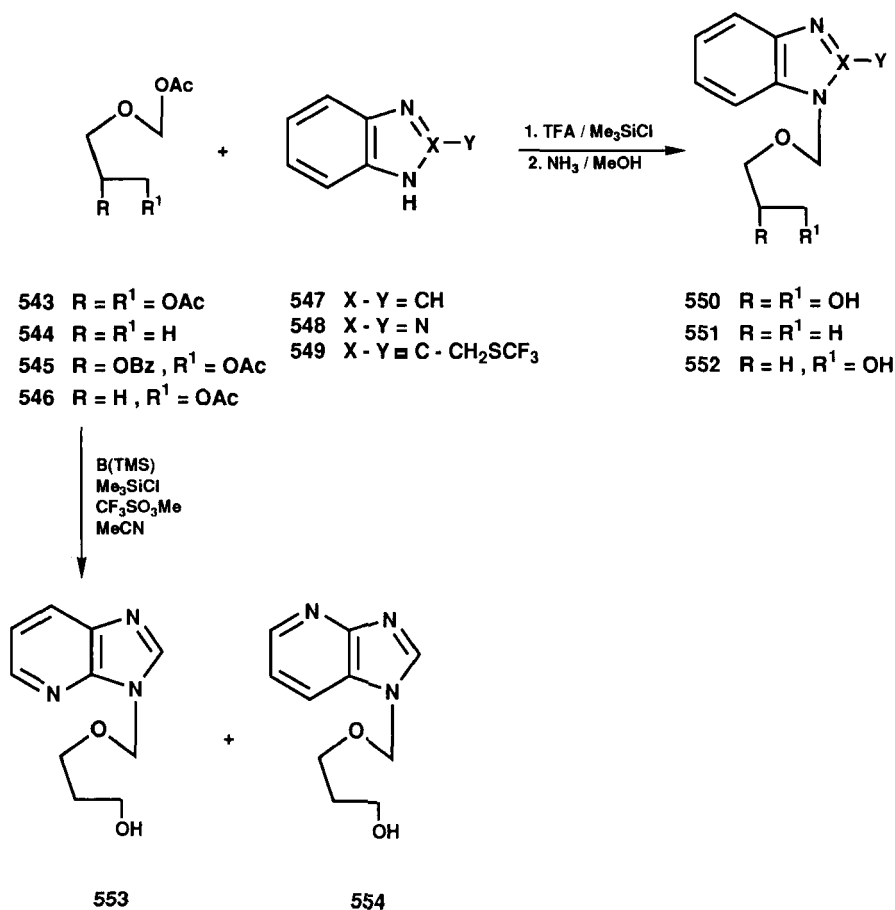
Acetoxymethyl ethers **539** and **540** could be prepared from the mixture of glycerol formal **537** and **538**. Reaction of **539** with GuAc_2 gave N-9 (**541**) (and N-7) guanine derivatives as racemic forms whose deacetylation gave **542** (84TL905; 85JMC926).

Alkylations of benzimidazole **547** and benzotriazole **548** with the triacylated derivatives **543** or **545** and their dideoxy derivative **544** gave after deprotection **550** and **551**, respectively (88KFZ714). The benzotriazoles had greater antiviral activity to enterovirus than the benzimidazoles. The acyclic derivatives derived from **549** are only moderately virucidal to some RNA-containing viruses (89KGS493). The reaction of **546** with 1(3)-*H*-imidazo[4,5-*b*]pyridine gave the 1- and 3-isomers **553** and **554** (90MI1). **552** was formed similarly.

The respective optical isomers (*R*)- and (*S*)-iNDG were prepared by reacting the enantiomers of the 1,2-di-*O*-benzylglycerols **556** and **565** with paraformaldehyde and anhydrous HCl to give the corresponding chloro-

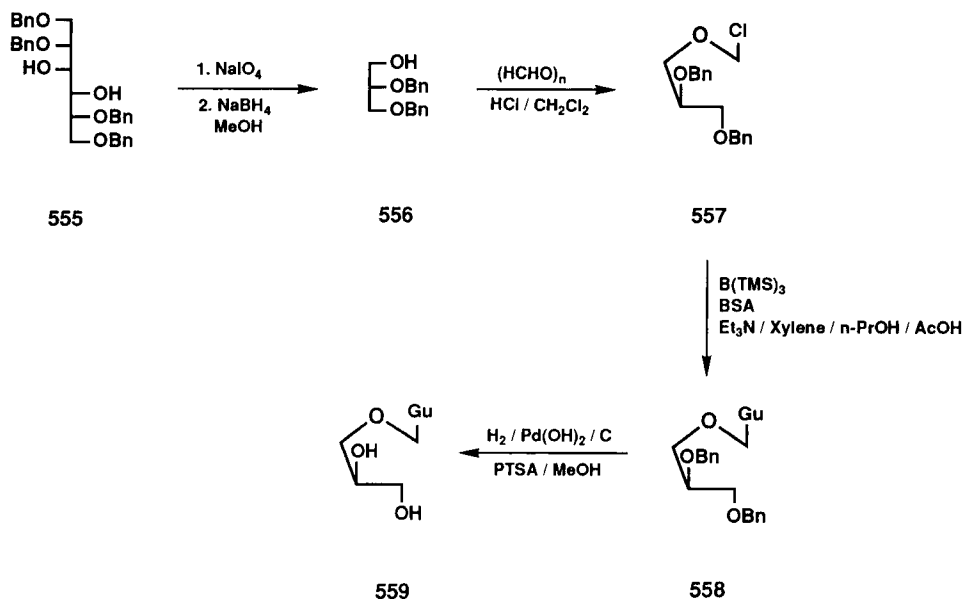


SCHEME 103



SCHEME 104

methyl ether **557** and its isomer **566**, respectively. They reacted with the tris (trimethylsilyl)guanine to give **558** and **567**, respectively. Their catalytic hydrogenation gave the corresponding **559** and **568** (85JMC926). The precursor for the chiral glycerol **556** was the D-mannitol derivative **555**, whose periodate oxidation and reduction gave **556**, whereas the other isomer **565** was prepared from the D-mannitol derivatives **560**, whose oxidation and reduction gave **561**. The last, upon benzylation and hydrolysis, gave **562**, which upon tritylation gave **563**; subsequent benzylation gave **564**. Hydrolysis then gave **565**. The racemic form exhibited potent antiviral activity (84TL905). The (*S*)-iNDG was found to be more active than the *R* enantiomer against HSV-1 and HSV-2 in cell culture; it had an ED_{50} comparable



SCHEME 105

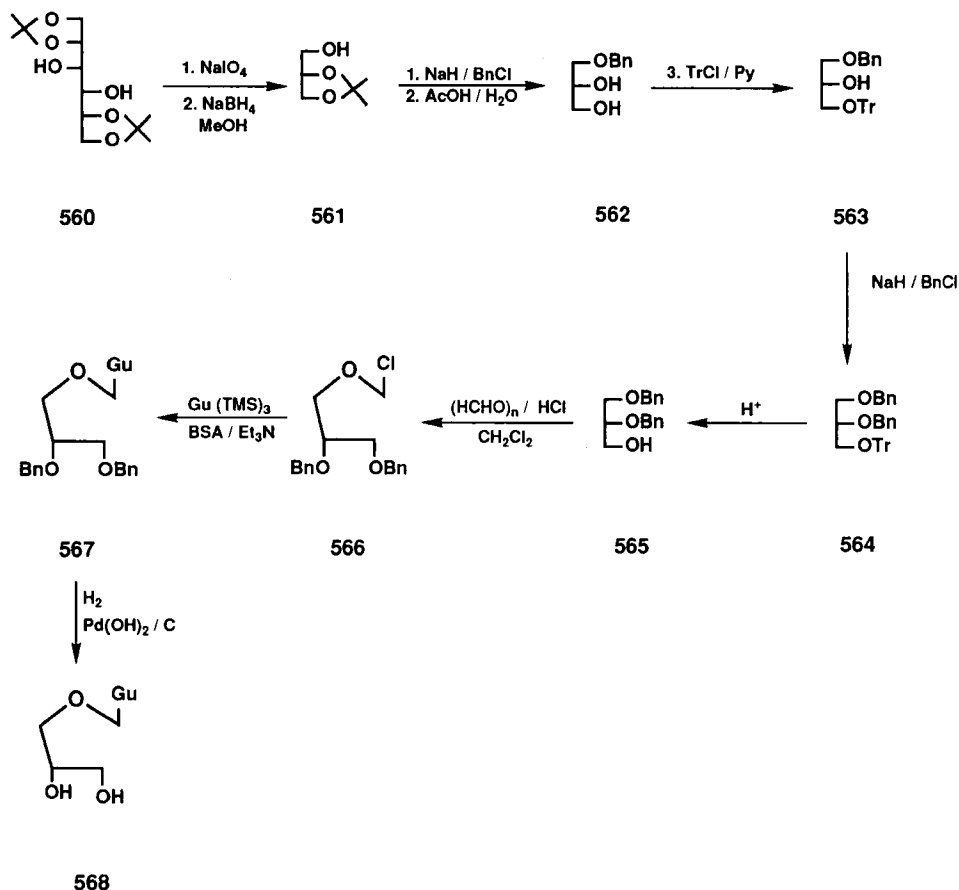
to those for ACV and 2' NDG. The inferior activity of (*R*)-iNDG paralleled the poor inhibition of viral DNA polymerase by its phosphorylation products. In mice (*S*)-iNDG was less efficacious than 2'NDG, but comparable to or more active than ACV (85EUP130126; 85JMC926).

An alternative source for the chiral nucleoside **559** utilizes methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside (**569**); this was chloromethylated to give **570**, which upon reaction with 2-amino-6-benzoyloxypurine gave **571**. Debenzylation of **571** gave **572**, whose periodate oxidation followed by reduction gave the glycerol derivative **573**, which upon acid hydrolysis gave **559** (85TL1815).

2. Deoxyazido and Deoxyamino Analogs

1-Hydroxy-2-azido-3-propoxymethylpyrimidines **577** were synthesized from **574** by displacement with azide ion to give **575**, followed by ring-opening with acetyl bromide to give **576**, which upon reaction with base and deacetylation gave **577** (89MI7).

The DL-serine uracil derivative **580** was prepared from DL-serine methyl ester hydrochloride by *N*-benzoylation to give **578**; chloromethylation gave **579**, which then was substituted by the silylated uracil (88ZOB2404).

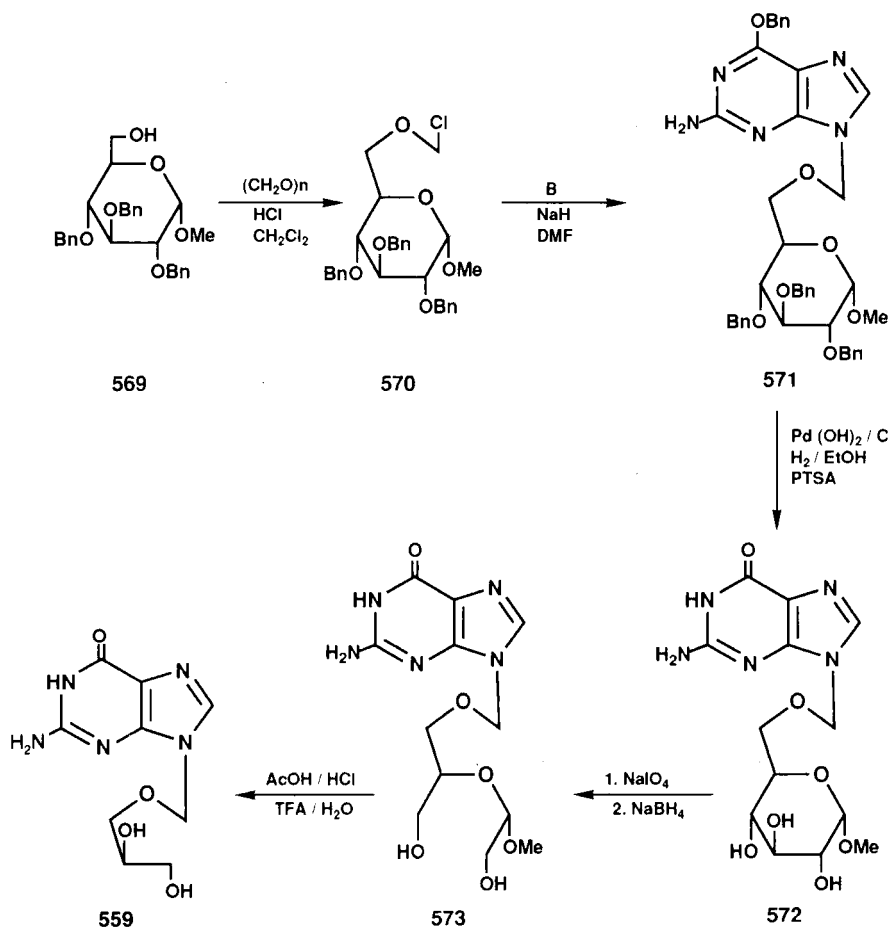


SCHEME 106

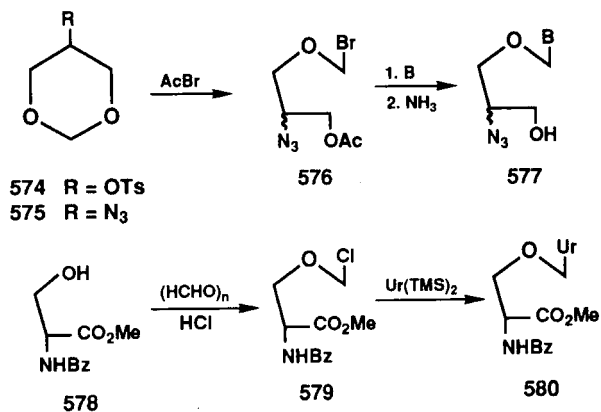
Reaction of the chloromethyl derivative **581** with a uracil derivative gave a mixture of **582** and **583** (91KFZ44).

3. Deoxy and Branched-Chain Analogs

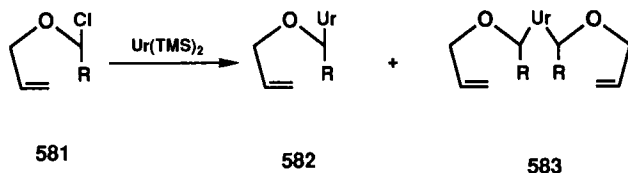
Selective benzylation of the triol **584** gave **585**, whose acetoxymethyl ether **586** condensed with diacetylguanine in the presence of bis(*p*-nitrophenyl) phosphate and sulfolane to give **587**, which upon deprotection gave **588** (86JMC1384). Another precursor for branched-chain nucleosides was pentaerythritol triacetate **589**, which upon chloromethylation gave **590**. Condensation of **590** with 6-chloropurine or *N*-acetylguanine gave a mixture



SCHEME 107



SCHEME 108



SCHEME 109

of the 7- and 9-isomers, whose deprotection gave **591**. The pyrimidine analogs were prepared from the silylated pyrimidine (84MI5). All showed activity against herpes viruses.

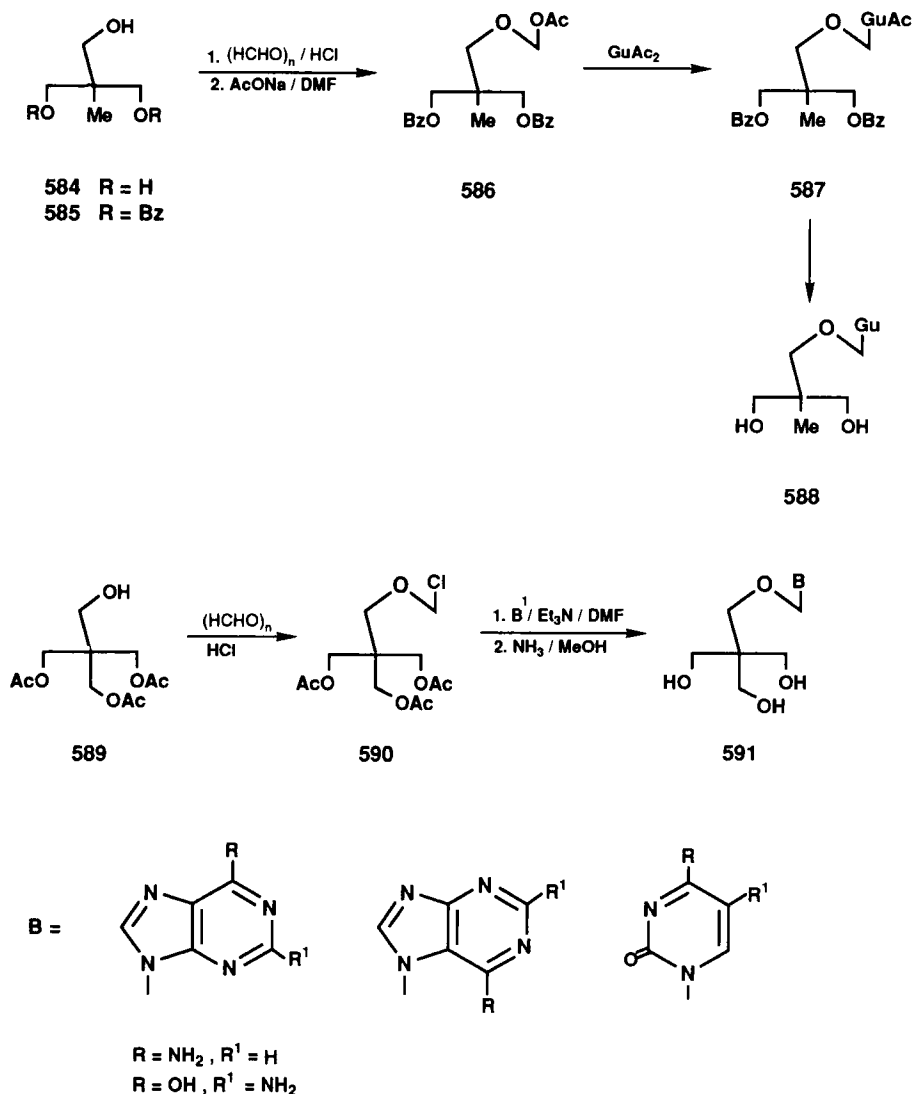
4. *Acyclo-C-Nucleoside Analogs*

The C-nucleoside analogs were prepared when 5-hydroxymethyluracil **592** and glycerine were condensed in the presence of HCl to give **593**, whose methylation with DMF–dimethylacetal gave **595**. Further reaction with guanidine gave the isocytidine analog **597**, which was purified via its acetyl derivative **596**. In contrast, methylation of **593** with HMDS/MeI gave **594**, whose separation was achieved *via* acetylation and deacetylation (86JHC1621).

Acyclic analogs of pyrazofurin were prepared by heating **422** with alcohol **598** in the presence of sodium acetate followed by deprotection and amidation to give **599**. The respective 3'-deoxy analog was also prepared from the respective alcohol and exhibited slight activity against human cytomegalovirus (91MI4).

5. *Translocation of the Oxygen with Carbon Analogs*

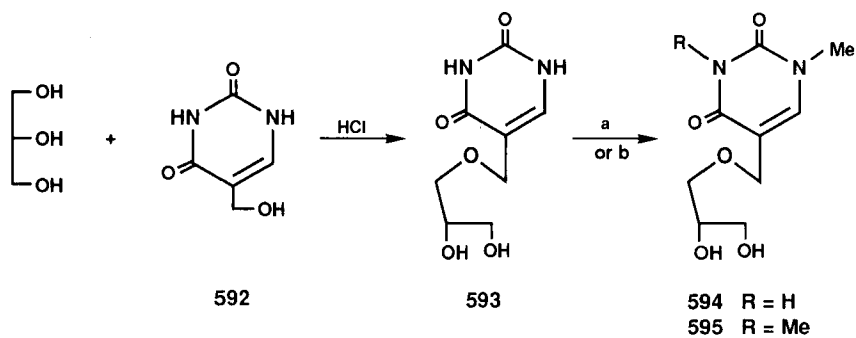
Translocation of the oxygen side chain with one of the two adjacent carbons could lead to two isomeric structures. Thus, nucleosides with C-1' translocated with the oxygen of the side chain have been synthesized. The need for protecting groups was obviated by introducing the hydroxy functionalities of the acyclic substituent at a later stage in the synthesis, by hydroxylation of an exocyclic double bond. Thus, cyclization of unsaturated ureas **600** gave the pyrimidines **602**, which, on treatment with osmium tetroxide and *N*-methylmorpholine *N*-oxide in aqueous acetone, gave the acyclonucleosides **603** [90JCS(P1)2175]. The guanine acyclonucleosides having 2,3-dihydroxybutoxy side chains were prepared via the alkenoxy amines **601** by condensation with 4,6-dichloro-2,5-diformamidopyrimidine to give **604**. Closure of the imidazole ring was achieved by heating with diethoxymethyl acetate followed by treatment with ammonia and *cis*-



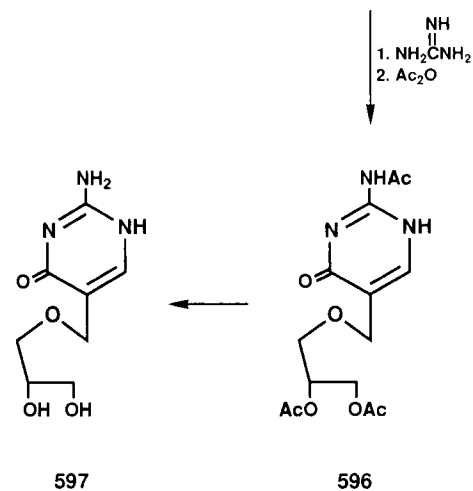
SCHEME 110

hydroxylation to give **605**, which upon treatment with formic acid gave **607** and upon catalytic hydrogenation gave **606**. Treatment of **605** with sodium methoxide gave the 4-methoxy derivative (91JMC57).

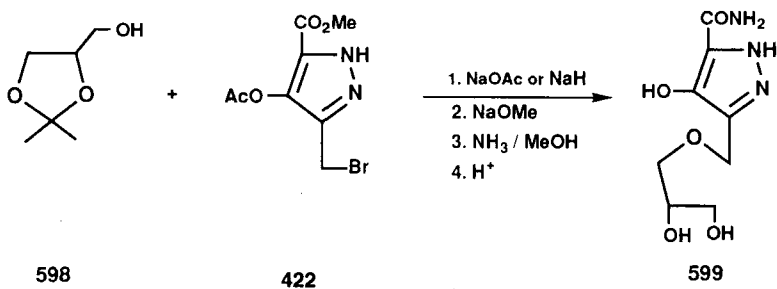
Nucleosides with a translocation of the oxygen with C-4' were prepared by coupling of the chloroacetate **608** with various bases, followed by depro-



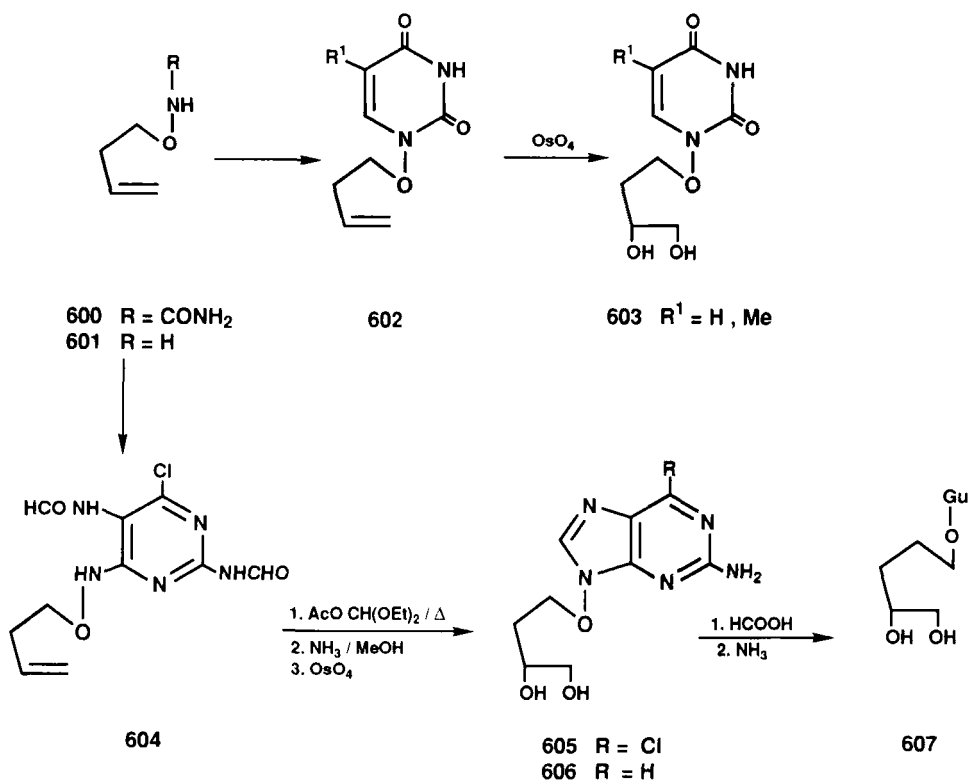
a = HMDS, MeI; b = DMFDMA



SCHEME 111



SCHEME 112



SCHEME 113

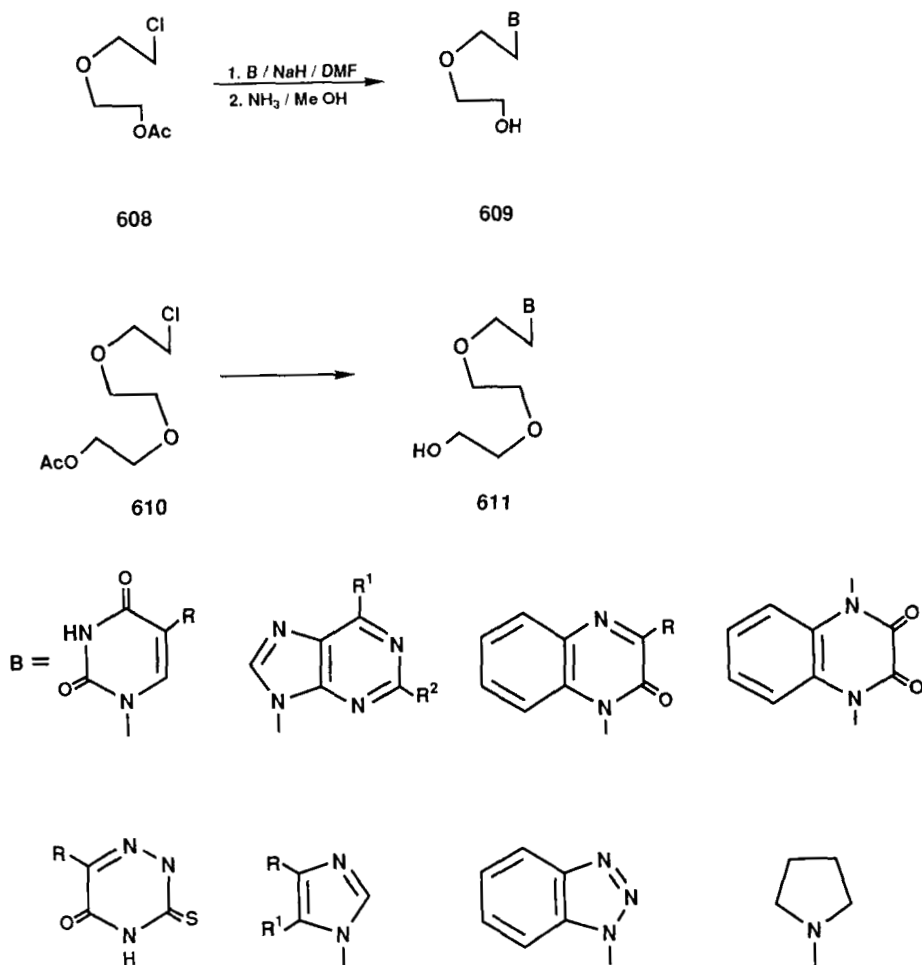
tection to give **609**. Similarly, the respective ethers **611** were prepared from **610** (89CS379; 96UP1).

C. 2',3'- AND 3',4'-*diseco*-NUCLEOSIDES (TYPE 2.3)

1. General Methods for Construction

Debenzoylation of the nucleoside analogs **612** gave **613**, which upon periodate oxidation and reduction gave the optically pure enantiomers **614**. Similarly, uracil analog **615** gave also the corresponding **614** (88KGS223).

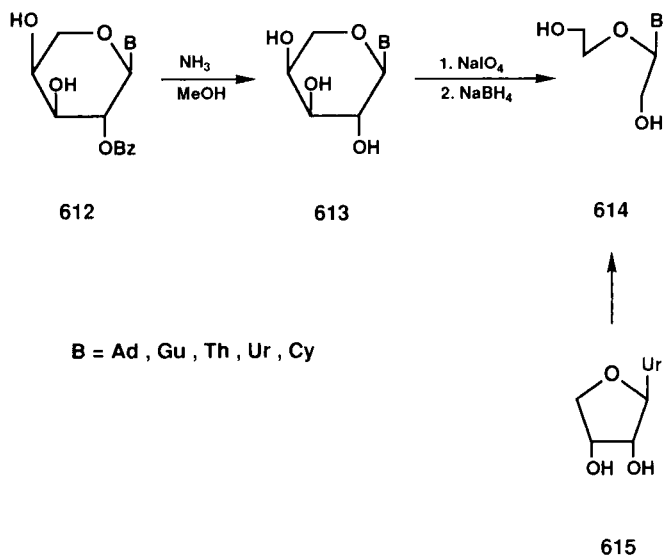
The racemic analogue **620** was prepared by alkylation of *N*-2,9-diacetylguanine with 2,3-dichlorotetrahydrofuran **616**. The adduct **617** was deacetylated to give **618**, and then monomethoxytritylated followed by



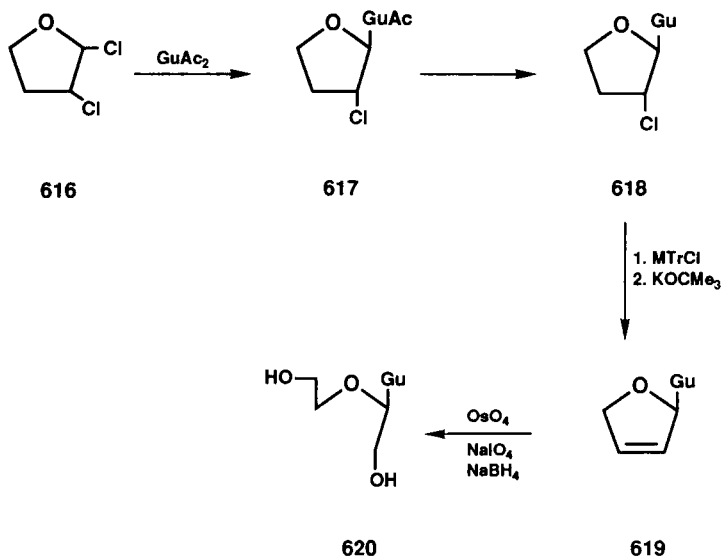
SCHEME 114

elimination of HCl to give **619**. Treatment of **619** with OsO₄-NaIO₄ and then reduction gave **620** (86CJC1885).

The racemic analogs were also obtained by replacement of the halogen atom in 2-chloromethyldioxolane **622**, obtained from ethylene glycol and **621**, by an acetoxy group to give **623**. Subsequent opening of the dioxolane ring with acetic anhydride in presence of ZnCl₂ gave **624**, followed by reaction with the base to give **625**. 1-Alkyl derivatives were almost the only product of the alkylation of trimethylsilyl derivatives of pyrimidine bases,

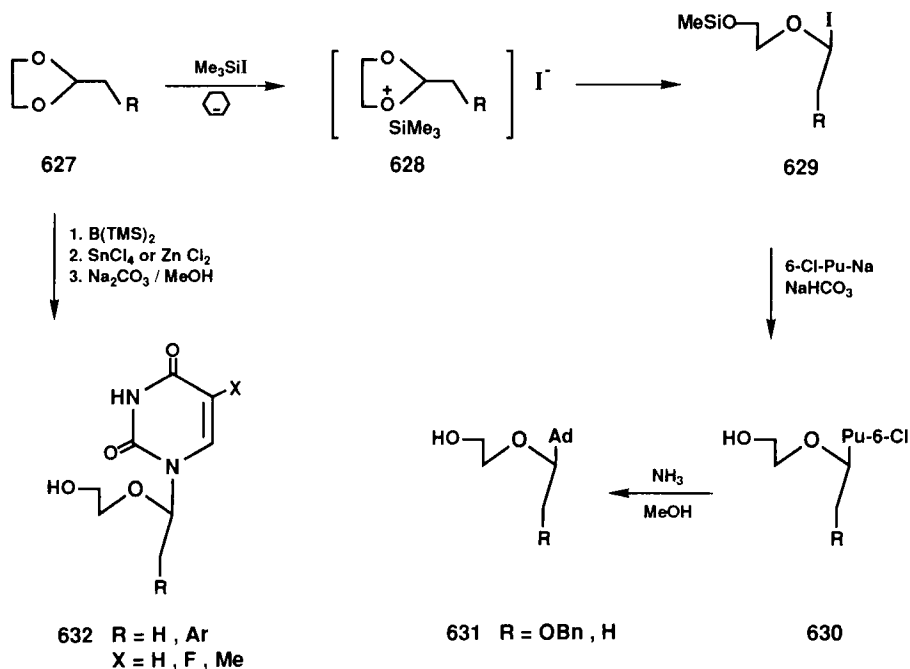


SCHEME 115



SCHEME 116

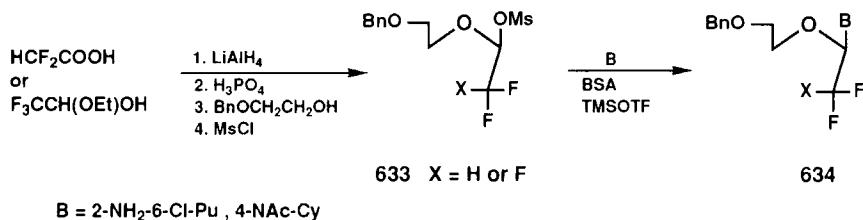
SCHEME 117



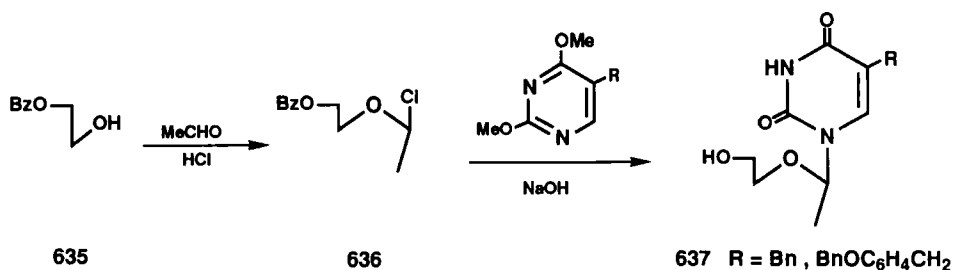
SCHEME 118

Reacting ethylene glycol monobenzoate **635** with acetaldehyde and HCl gas gave **636**, whose reaction with pyrimidine derivatives followed by de-benzoylation gave **637** (86JHC1651). The base-catalyzed hydrolysis of 6-substituted 9-(1-ethoxyethyl)purines takes place by nucleophilic attack of hydroxyl ion on C-8 of the purine moiety [82ACSA(B)707].

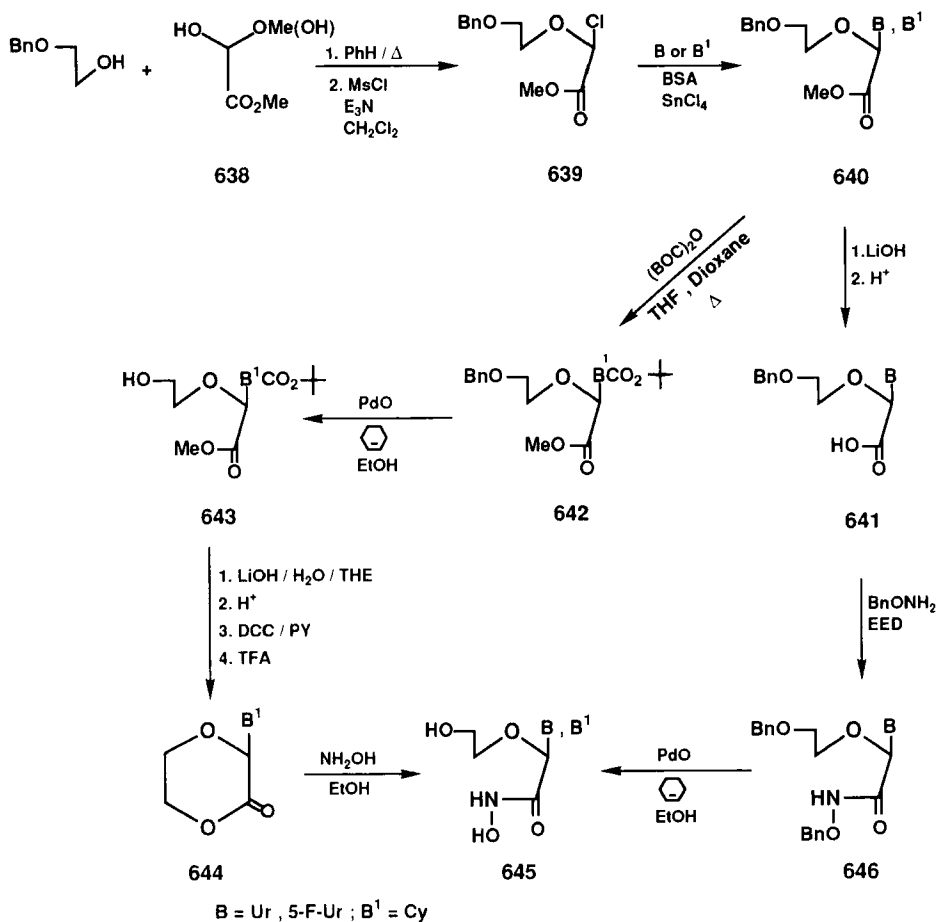
Condensation of 2-(benzyloxy)ethanol with a mixture of the hydrate and methyl hemiacetal of methyl glyoxalete **638** gave a hemiacetal, which was converted directly with methanesulfonyl chloride to α -chloro ether **639**. It condensed with silylated uracil, 5-fluorouracil, and N^4 -acetylcytosine,



SCHEME 119



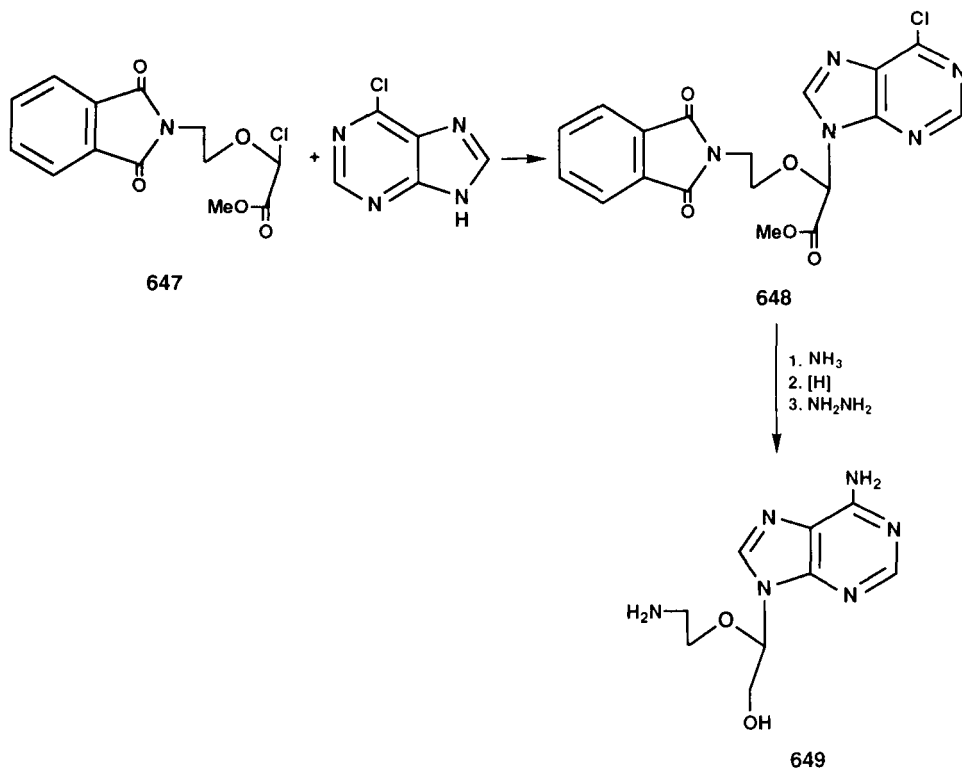
SCHEME 120



SCHEME 121

generated *in situ* from the bases and *N,O*-bis(trimethylsilyl)acetamide (BSA), in presence of stannic chloride to give pyrimidine acyclonucleosides **640**. Reaction of the ester with NH_2OH was unsuccessful. Therefore, the esters were saponified to the corresponding acids **641** and then coupled to *O*-benzylhydroxylamine to give **646**. Didebenzylation of a uracil derivative was smoothly accomplished with PdO-catalyzed transfer hydrogenation. However, the 5-fluoro derivative could not be obtained in sufficient purity. This problem required the development of a mild method generating the hydroxamic acid as the final step in the synthesis. Lactones seemed ideally suited for this purpose. Catalytic transfer hydrogenation of **642** gave **643**; this, upon lactonization, gave **644**, which reacted with NH_2OH to give **645**. The hydroxamates inhibited CDP reductase activity (89JMC1879).

The ring-opened analog of 5'-aminocordycepin was prepared by reaction of 6-chloropurine with phthalamide **647** to give **648**, which upon conversion of the chloro substituent to amine, reduction of the ester group, and hydrazinolysis gave **649** (87MI1).



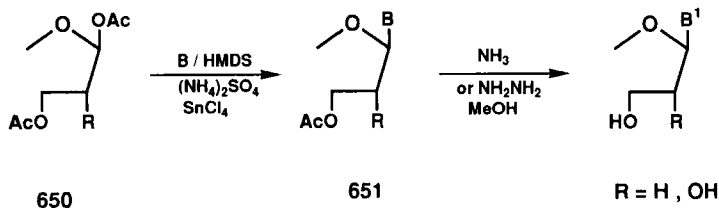
SCHEME 122

D. 3',4'- AND 4',5'-*diseco*-NUCLEOSIDES (TYPE 2.4)1. *Typical Examples*

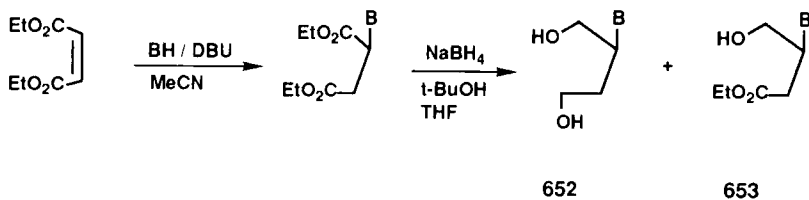
Reaction of 2,3-diacetoxy-1,1-dimethoxypropane and 1,3-diacetoxy-1-methoxypropane **650** with bis-*O*-trimethylsilyluracils and *N,O*-bis-trimethylsilyl-*N*-acetylcytosine in the presence of stannic chloride, a modification of the Helbert–Johnson reaction, gave **651**. Also, 2,3-divaleryloxy-1,1-dimethoxypropane was used (85MI6). Similarly, reaction of pertrimethylsilyl derivatives of *N*-benzoyladenine with 1,2,3-triacetoxy-1-methoxypropane gave N-9 and N-7 isomers, whereas the reaction with 1,3-diacetoxy-1-methoxypropane afforded the N-9 isomer (87MI3). Nucleoside analogs of 2-*N*-acetylguanine, hypoxanthine, and diacetamide purine were also prepared (87MI3). Acetyl groups were subsequently removed from most of the protected analogs by treatment with ammonia in aqueous methanol, except in the case of 5-trifluoromethyluracil, which gave the 5-cyano derivative. Because fluoride ion is normally a poor leaving group in displacement and elimination reactions, direct displacement of fluoride by ammonia seemed unlikely, and a more plausible mechanism for this transformation involved initial attack of ammonia at C-6. 2,3-Bis(trimethylsilyloxy)-1,1-dimethoxypropane was used where subsequent removal of the *O*-trimethylsilyl groups under neutral aqueous conditions was required. Under the reaction conditions employed, condensation of bis-*O*-trimethylsilyl-5-nitrouracil and *N,O*-bis-trimethylsilyl-*N*-acetylcytosine with 1,3-diacetoxy-1-methoxypropane afforded, not only the 1-*N* alkylated products, but also the 1,3-disubstituted pyrimidines. The activity of these acyclonucleosides was studied toward influenza A, parainfluenza type 1, and herpes simplex type 1 viruses.

2. *Carboacyclic Analogs*

Michael addition of nucleobases to diethyl maleate followed by reduction gave **652** and **653** (92MI6). The uracil analog exhibited only marginal activity against HIV.



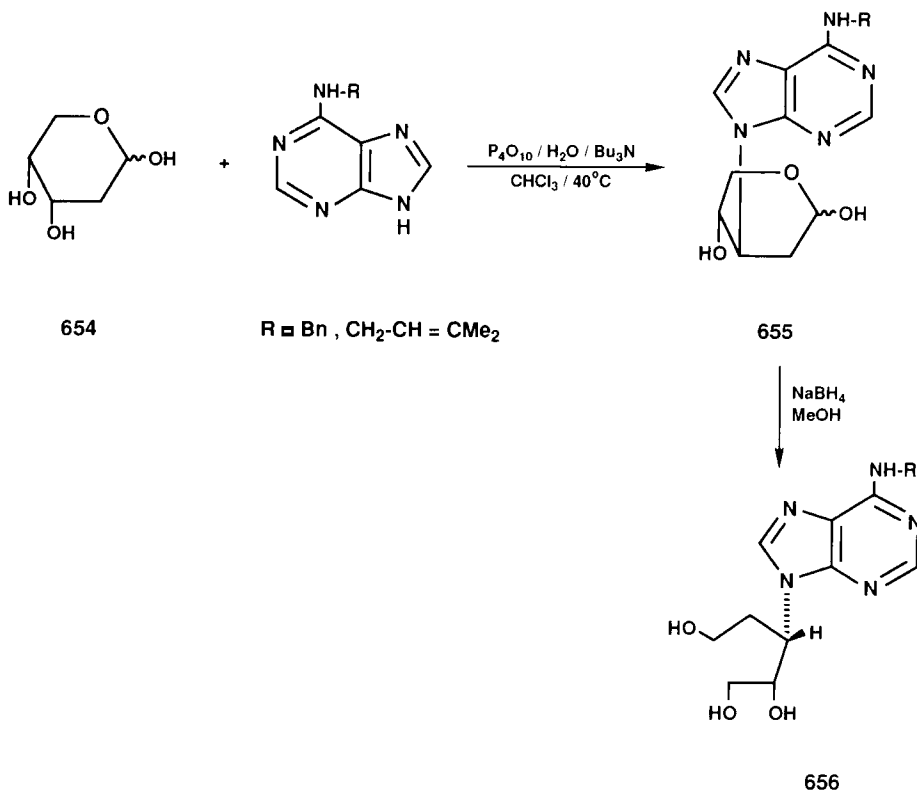
SCHEME 123



B = Ad , Cy , Th , Ur , Gu

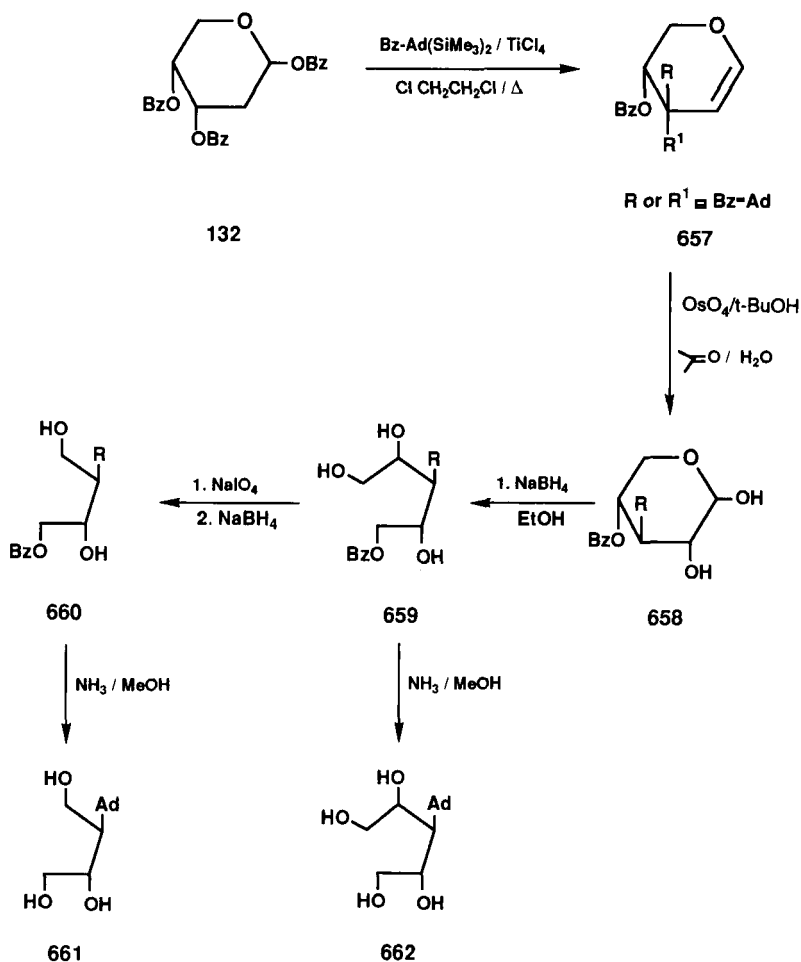
SCHEME 124

Condensation of *N*-alkyladenine with 2-deoxyribose (**654**) in a phosphorus pentoxide mixture gave **655** via a probable Michael-type addition to an α,β -unsaturated sugar aldehyde formed *in situ* from 2-deoxyribose. Reduction of **655** gave **656** (92JHC511). Neither **655** nor **656** showed any significant activity against HSV-1.



SCHEME 125

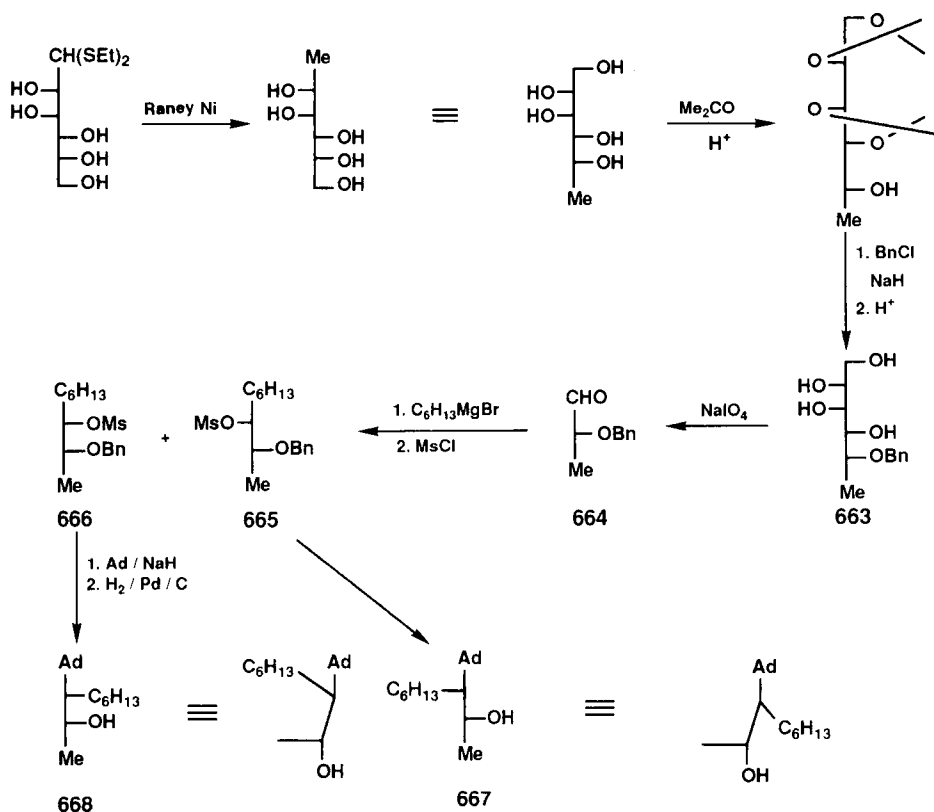
Reaction of 1,3,4-tri-*O*-benzoyl-2-deoxy-D-ribofuranose (**132**) with the silyl derivative of benzoyladenine in the presence of TiCl_4 gave a mixture of **657**. They were also formed by reaction of the respective 1-chlorosugar with the adenine derivative. The high reactivity of the sugar derivative resulted in a facile elimination of hydrogen chloride. *Cis*-hydroxylation of one of the isomers of **657** gave an anomeric mixture of **658**, whose reduction gave **659**; a migration of the benzoyl group had taken place. Debenzoylation of **659** gave **662**, whereas its periodate oxidation and reduction gave **660**, which upon debenzoylation gave **661** (91T9993).



SCHEME 126

3. EHNA Analogs

The acyclicnucleoside *erythro*-9-(2-hydroxy-3-nonyl)adenine (74JMC6; 78MI1) is abbreviated as EHNA. Because of its importance as an inhibitor of adenosine deaminase, various approaches were reported for the synthesis of the chiral isomers (81JMC1383, 81MI1; 82JOC2179, 82MI2; 88JMC390). Thus, the synthesis of both isomers of EHNA from D- and L-rhamnose was reported (82JOC2179). Scheme 127 depicts those derived from D-rhamnitol. The key intermediate *R*-2-(benzyloxy)propanal (**664**) derived from 5-*O*-benzyl-D-rhamnitol (**663**) was condensed with hexylmagnesium bromide to give a 3:1 mixture of threo/erythro alcohols. Both were converted to the respective mesylated products **665** and **666**, whose displacement with (adenin-9-yl) sodium salt gave the erythro **667** and threo **668** isomers of EHNA, respectively. A similar sequence was also depicted for the other two isomers from L-rhamnitol.



SCHEME 127

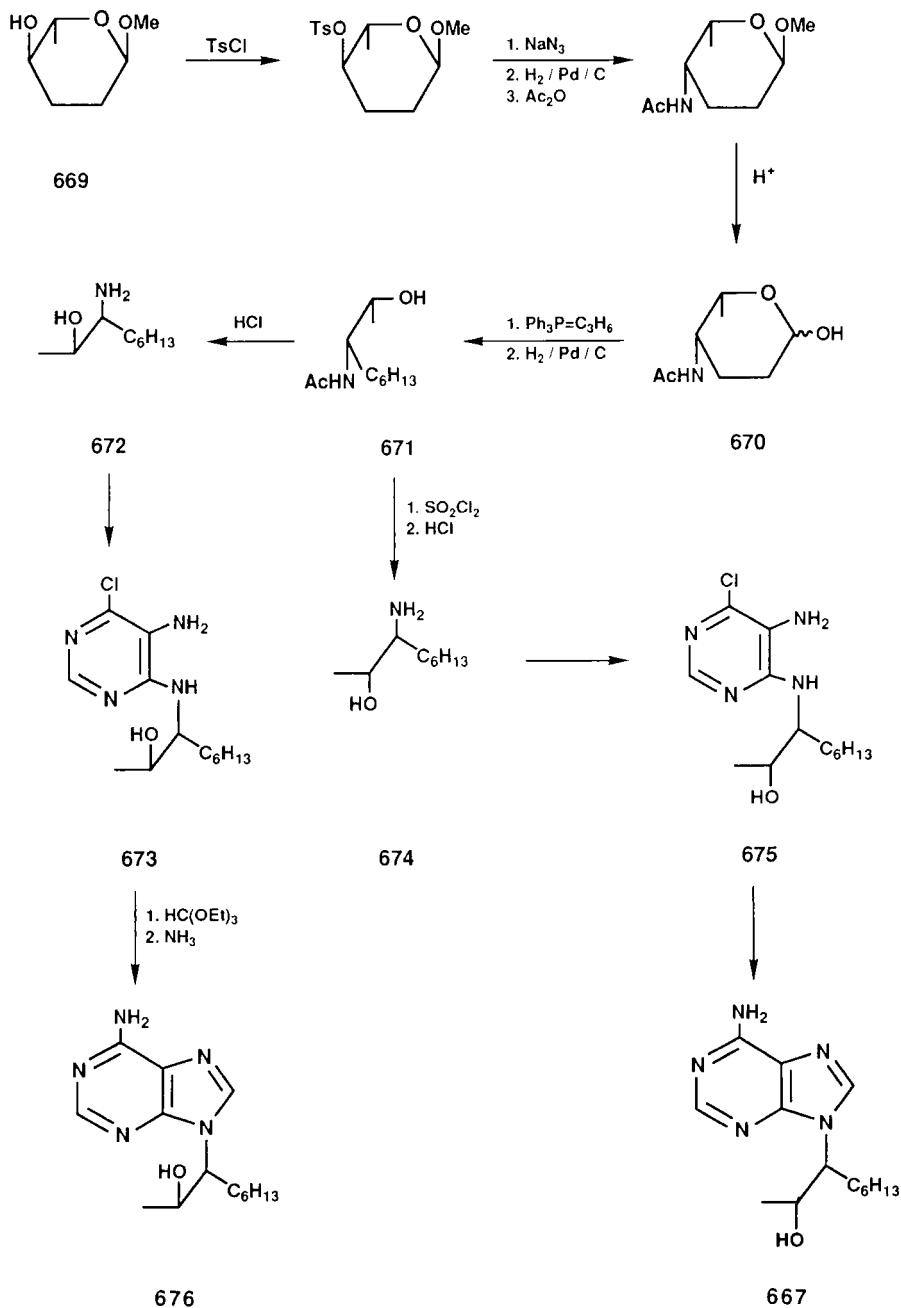
Alternatively, the heterocyclic ring was built onto an amino alcohol precursor that is derived from the sugar precursor methyl-L-amicetoside (**669**), obtained from L-rhamnose, by tosylation followed by azide displacement, reduction, acetylation, and then hydrolysis to give **670**. Reaction of **670** with a Wittig reagent gave the acetylamino alcohol **671**, whose hydrolysis with HCl gave the *threo*-aminoalcohol (2*S*,3*S*)-**672**. However, treatment with thionyl chloride prior to hydrolysis with HCl resulted in the inversion of configuration of C-2 by an S_N1 mechanism, involving an oxazoline intermediate to provide the erythro isomer (2*R*,3*S*)-**674**. The other two isomers could be prepared from methyl α -rhodinoside, obtained from **669** by an inversion of configuration at C-4, by a similar sequence of reactions on **669** shown in Scheme 128 (81JMC1383). The amino alcohols were converted to their respective adenine analogs by condensation with 5-amino-4,6-dichloropyrimidine to give **673** and **675**, which was followed by cyclization and reaction with ammonia to give **676** and **667**, respectively (74JMC6).

The chiral aminoalcohol precursor for the synthesis of EHNA analogs could be obtained from L-ascorbic acid, whose isopropylidenation gave **677**, which was transformed via degradation and esterification to **678** (84TL3841). Reduction of **678** followed by tosylation and epoxide formation gave **679**. Addition of pentylmagnesium chloride followed by mesylation gave **680**, whose azide displacement and reduction gave **681**. Further conversion to the 3-deaza analog **685** was achieved via **682**. Conversion of **681** to **684** was also achieved via **683**. Reductive periodate cleavage of **684** gave **686**, which was converted to the fluoro analog by treatment with DAST. In contrast, the respective chloro and bromo derivatives were prepared via the corresponding tosylate by treatment with Bu₄NX.

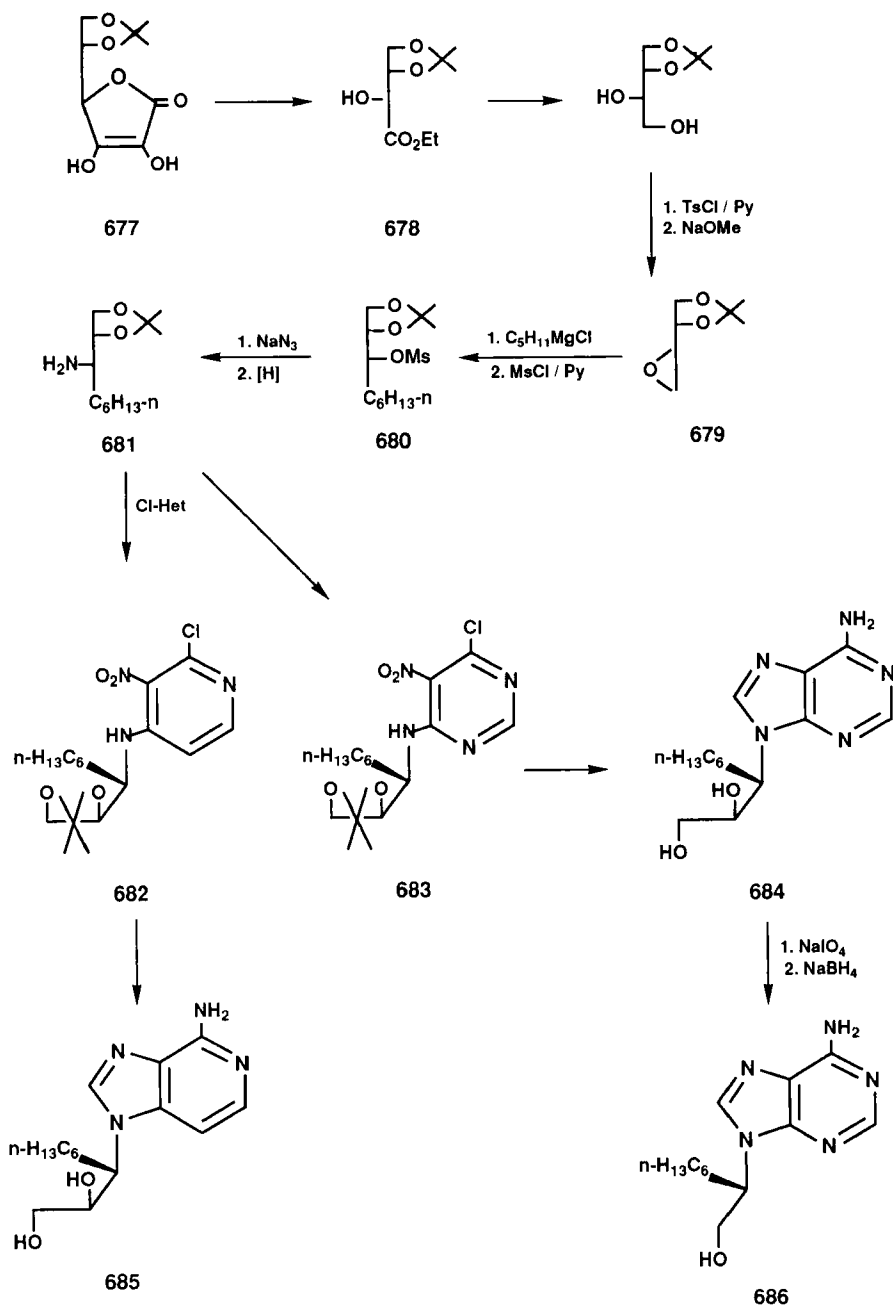
The erythro isomer could also be prepared from **679**. Thus, reduction of **679** followed by benzylation and then hydrolysis gave **687**, whose tosylation and treatment with base gave the respective epoxide, which upon addition of 1-pentenyl-5-magnesium bromide gave **688**. Conversion of the alcoholic group in **688** to an amino group was achieved by a Mitsunobu reaction to the azido group followed by reduction. Amination of the chloroheterocycle followed by reduction and cyclization gave **689**. Amination, hydroboration, and debenylation then gave **690**.

The 7-deaza EHNA analog **691** was obtained by condensation of 4,6-dichloropyrimidine-5-acetaldehyde with **674**. The 1,3-dideaza EHNA analog was prepared from erythro-3-amino-2-nonanol (**674**) by condensation with 1-chloro-2,3-dinitrobenzene, prepared in turn from 1-amino-2,3-dinitrobenzene, to give **692**. Reduction followed by cyclization with formamidine acetate gave **693** (88JMC390).

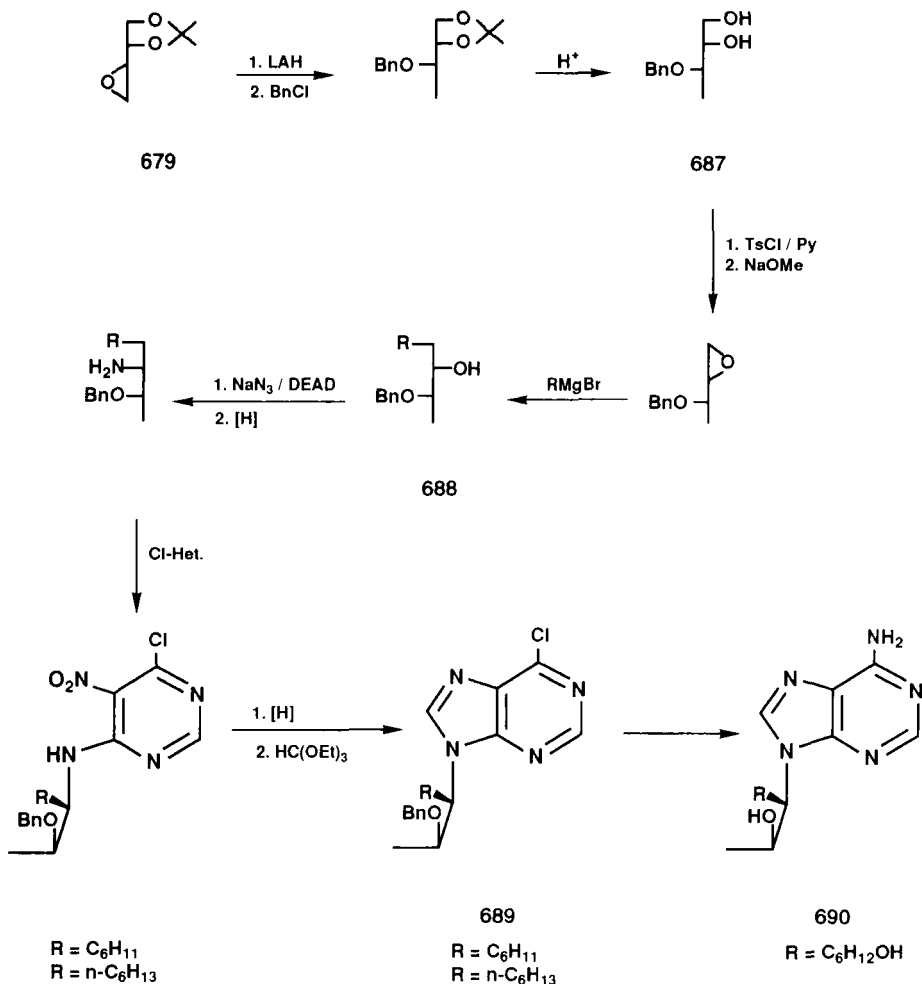
As a further modification of EHNA, condensation of ethyl-2-amino-2-cyanoacetate or aminomalononitrile with erythro-3-amino-2-nonanol in



SCHEME 128



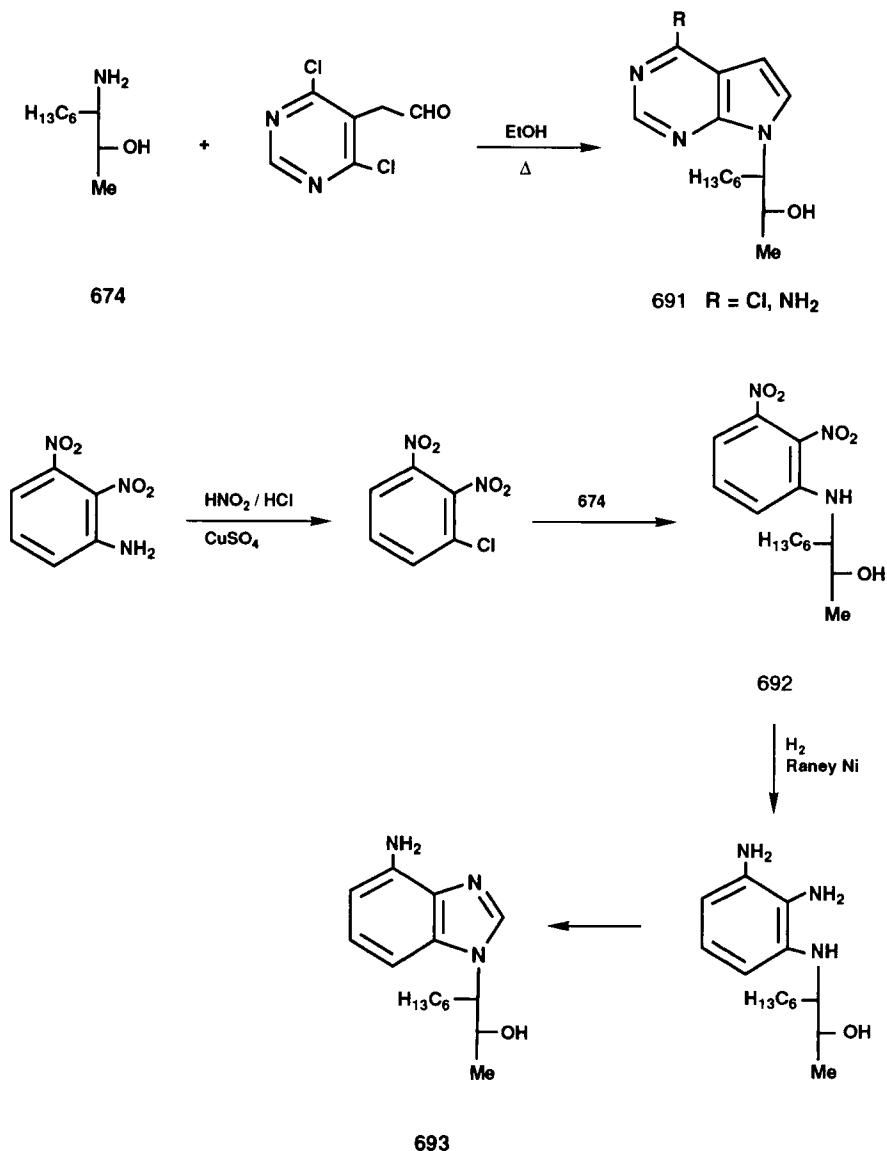
SCHEME 129



SCHEME 130

presence of triethyl orthoformate gave imidazole derivatives. Chemical modification of the two substituents afforded a variety of analogs (91JMC1187).

EHNA in its racemic form was designed as a semitight binding inhibitor of ADA. The synthesis of the chiral isomers allowed identification of the (+)2*S*,3*R* as the most potent ADA inhibitor. This led to enhancement of ara-A activity against human pancreatic and colon carcinomas. (+)EHNA has a short duration of action, and it is believed to be metabo-



SCHEME 131

lized by a cytochrome P-450 mediated hydroxylation in the nonyl side chain. The 3-deaza(\pm)EHNA had comparable activity to (\pm)EHNA (84JMC274; 88JMC390). EHNA has the antineoplastic activity of adenosine analogs against human pancreatic DAN and human colon HCT-8 carcinomas (88MI1).

E. 4',5'- AND 4',*x*-*diseco*-NUCLEOSIDES (TYPE 2.5)

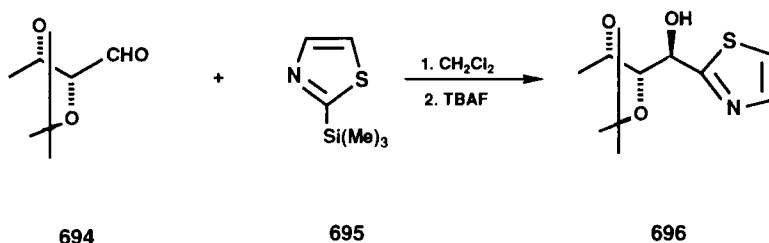
Although typical examples of this type are few, the respective 4'-hydroxylated analogs are frequently prepared. During work aiming to elongate the sugar chain, thiazole nucleoside **696** was prepared by an anti-diastereoselective addition of 2-trimethylsilylazoles (thiazole, benzothiazole, oxazole) **695** to asymmetric aldehydes **694** to give the corresponding *O*-silylcarbinols in high stereoselectivity (85TL5477; 89JOC693).

Condensation of D-ribonolactone (**698**) with 2-(3,4-methylenedioxyphenyl)ethylamine (**697**) gave an amide **699**, whose acetylation with Ac₂O in pyridine and subsequent oxidation with *m*-chloroperbenzoic acid gave nitron **700**, which was then hydrogenated in an acetic acid-HCl mixture over Adams catalyst and acetylated *in situ* to give **701** and **702** isolated by chromatography [92JCR(S)402].

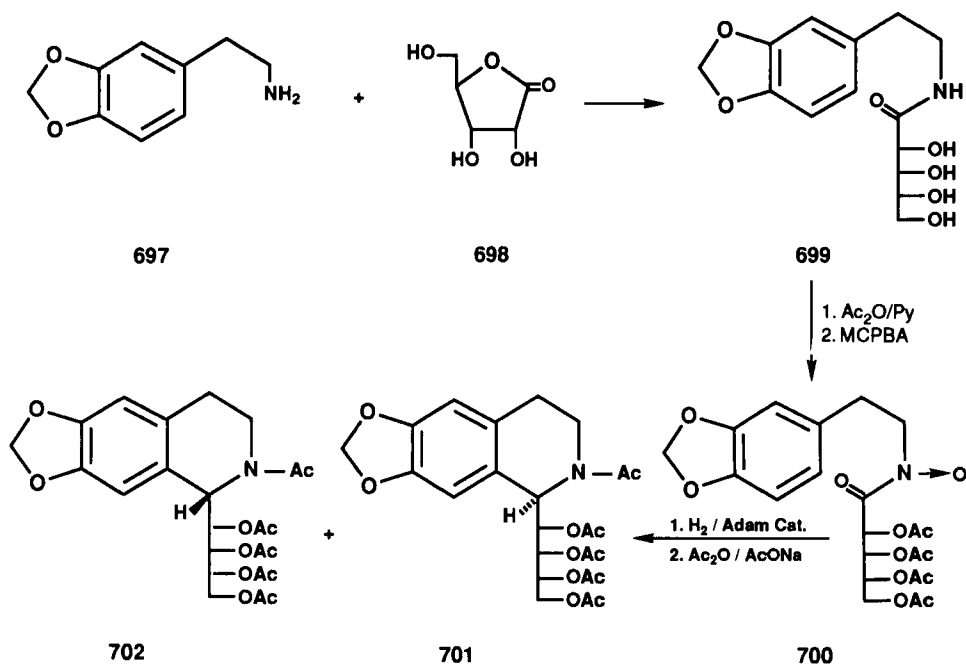
The reaction of aminosugar **704** with isocyanates and isothiocyanates has been studied extensively (85AQ(C)147; 91MI2, 91MI3). The reaction gave **703** via the formation of a ureido derivative, which is too reactive to be isolated. The formation of **705** from **704** during the acetylation and deacetylation was studied.

Reaction of 1-amino-1-deoxy-D-arabino hexulose **706** with cyanamide gave the imidazolin-2-ylideneammonium picrate **707** (89MI2).

The reaction of D-glucosamine **704** with 1,3-dicarbonyl compounds either in an acyclic structure or in a cyclic form gave **708** (84MI1; 85MI2; 92MI3).



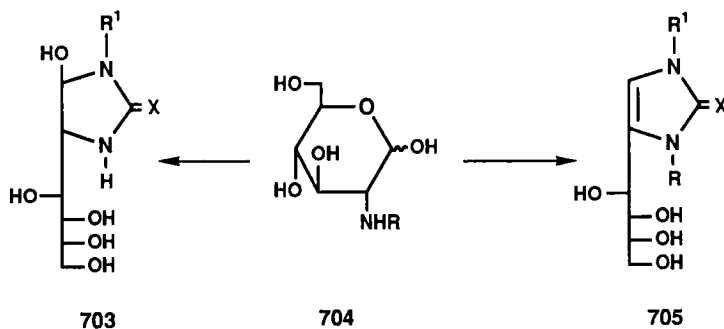
SCHEME 132



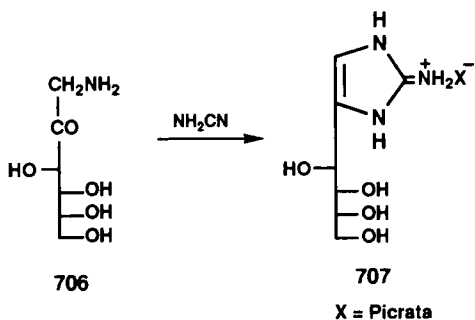
SCHEME 133

The 1,2,3-triazoles **710** readily obtained from osazones **709** could be reacted with HBr/AcOH to give **711** (96UP2).

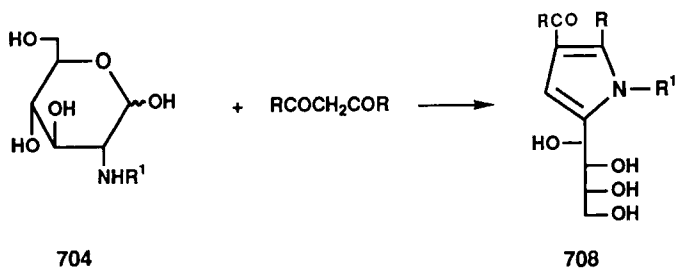
Reaction of per-*O*-benzoyl aldononitriles **712** with ammonium azide gave the tetrazole benzoate **713**, whose debenzoylation gave **714**. Other analogs with a different configuration were also prepared (79MI1).



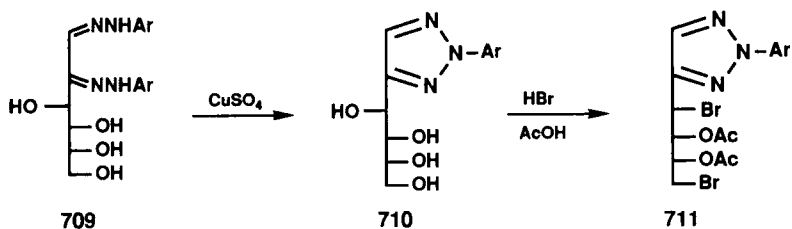
SCHEME 134



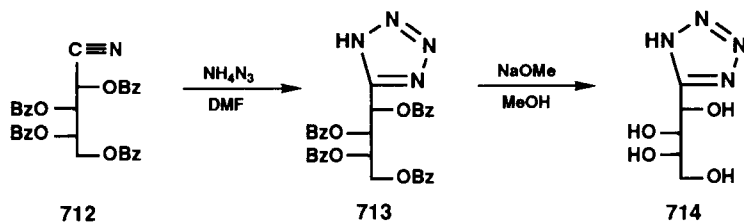
SCHEME 135



SCHEME 136



SCHEME 137

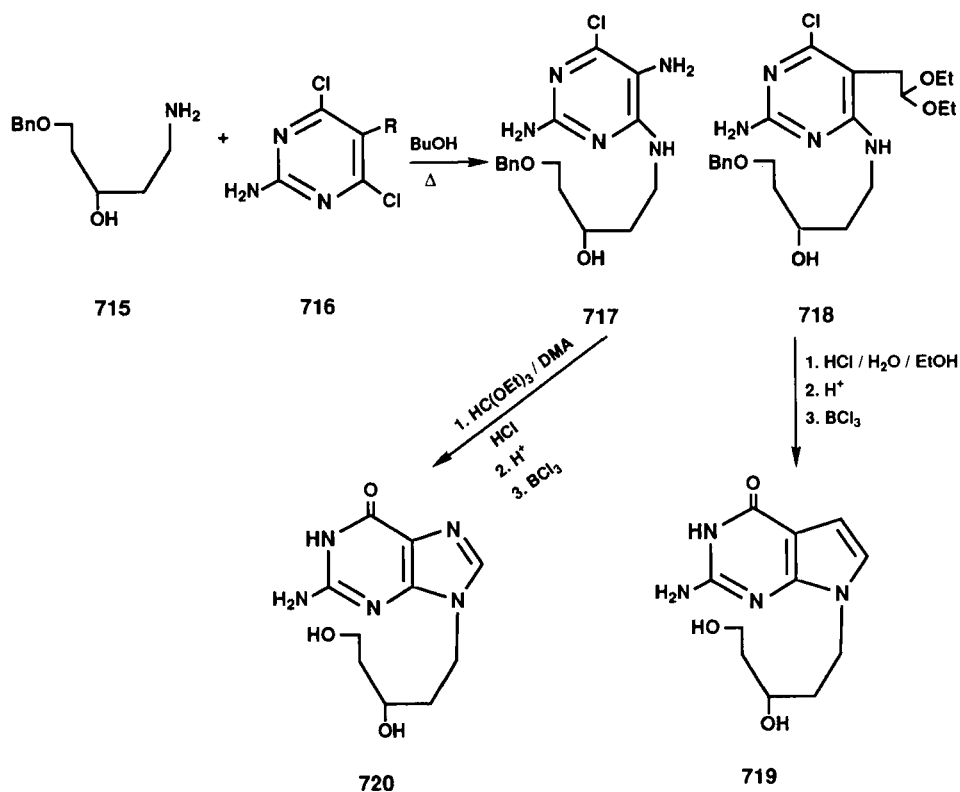


SCHEME 138

F. 1',*x*- AND 4',*x*-diseco-NUCLEOSIDES (TYPE 2.6)

The starting material was prepared by benzylation of but-3-en-1-ol followed by epoxidation with MCPBA to give an epoxide, whose ring opening was achieved with trimethylsilyl cyanide in the presence of diethylaluminum chloride to give a hydroxy nitrile derivative. Complete reduction of the nitrile with lithium aluminum hydride in diethyl ether led to **715**, which was condensed with 2-amino-4,6-dichloro-5-(substituted)pyrimidine (**716**) to produce **717** and **718**, depending on the substituent R. The latter, upon acidic hydrolysis and removal of the benzyl group, gave **719**. The synthesis of guanine analog **720** was achieved by cyclization of **717** followed by hydrolysis and deprotection (90JMC2476).

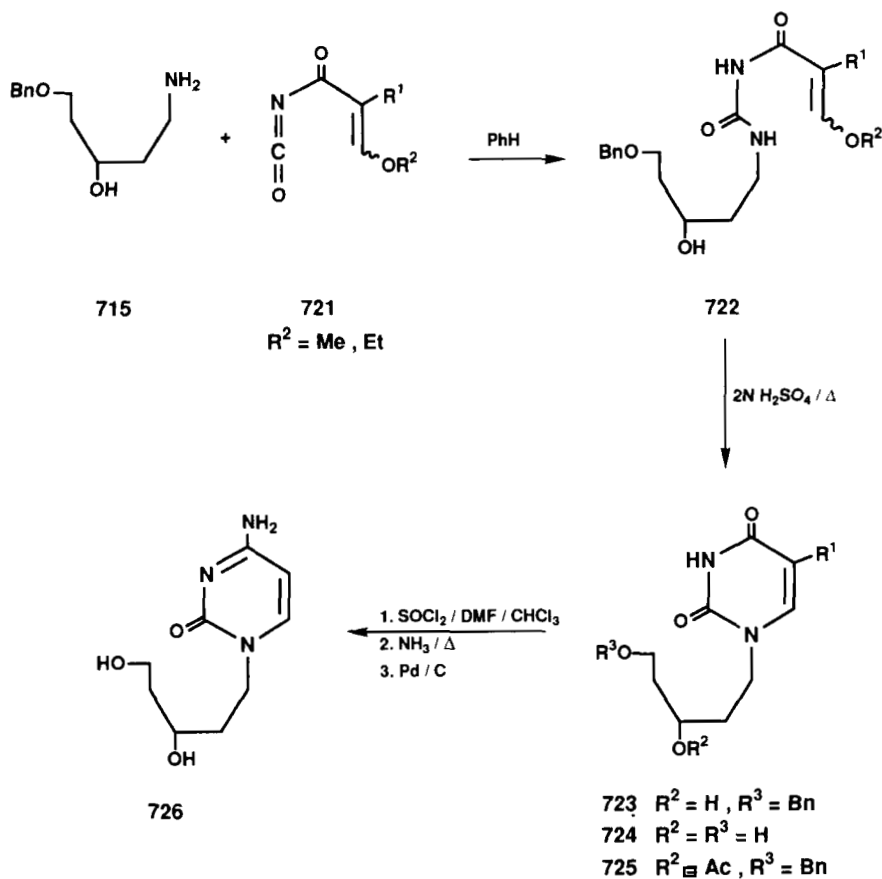
The cytosine analog **726** was synthesized by reacting **715** with isocyanate **721** to give **722**. Cyclization then gave **723**, which was deprotected to form



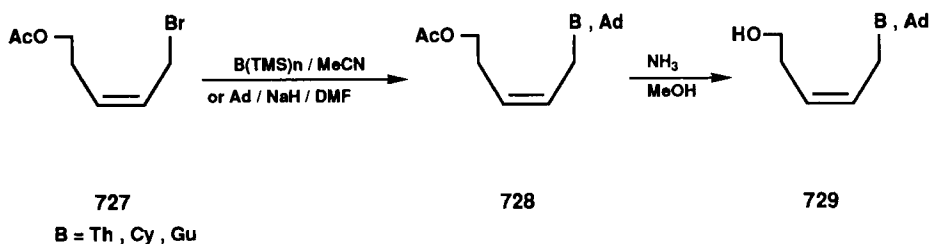
SCHEME 139

724. The cytidine analog was prepared from **725** by chlorination, aminolysis, and deprotection to give **726** (90JMC2476). The compound displayed no anti-HIV activity, indicating that replacement of the carbohydrate moiety of the different naturally occurring nucleosides by a pentane-3,5-diol chain does not give rise to antiviral activity against HSV-1, HCMV, and HIV-1.

Acyclic nucleoside analogs were prepared containing C-5' hydroxyalkyl fragments, where the distance between the 5'-hydroxyl group and the heterocyclic moiety corresponds to that in dideoxydidehydronucleosides (as confirmed by computer modeling). Condensation between 5-*O*-acetyl-1-bromo-2-pentene (**727**) and persilylated heterocyclic bases (pyrimidines and guanine) or adenine sodium salt gave rise to the acyclic nucleosides **728**. Deprotection by NH_3/MeOH gave the desired nucleosides **729** (91MI1).



SCHEME 140



SCHEME 141

G. 1',*x*- AND 4',5'-*diseco*-NUCLEOSIDES (TYPE 2.7)

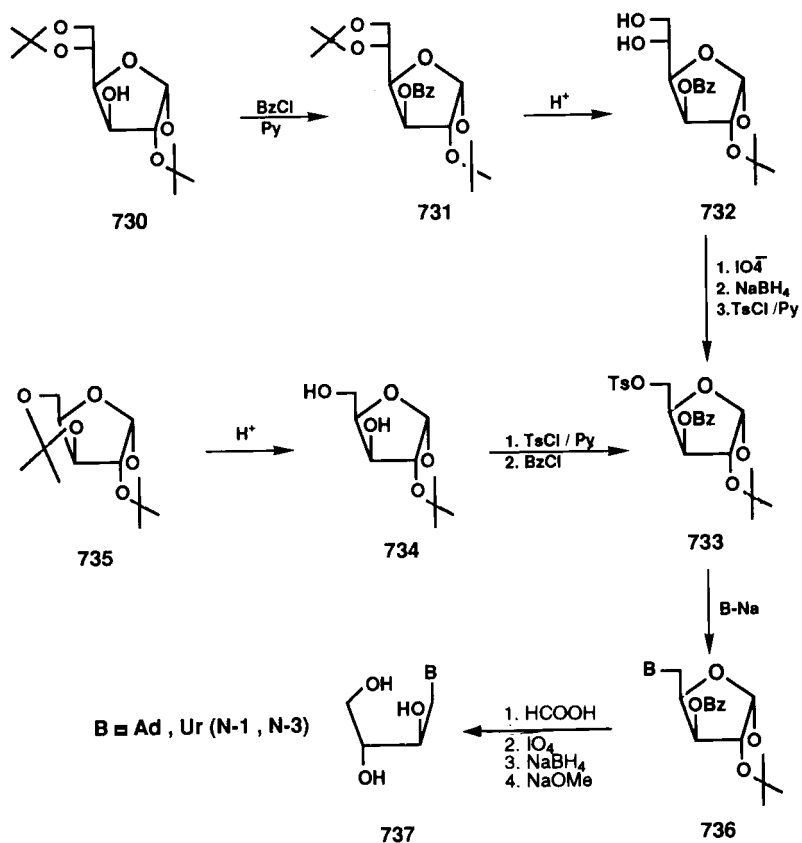
1. *Acyclo-N-Nucleoside* Analogs

The starting **733** could be prepared from the D-glucose derivative **730** by benzylation to **731**, followed by partial deisopropylidenation to **732** and then periodate oxidation, reduction, and tosylation. Alternatively, it was formed from the D-xylose derivative **735** by partial hydrolysis to **734**, followed by tosylation and then benzylation. Reaction of **733** with the sodium salt of bases gave **736**. Hydrolysis of the isopropylidene group followed by periodate oxidation, reduction, and then debenzoylation gave **737** (79CCCC593).

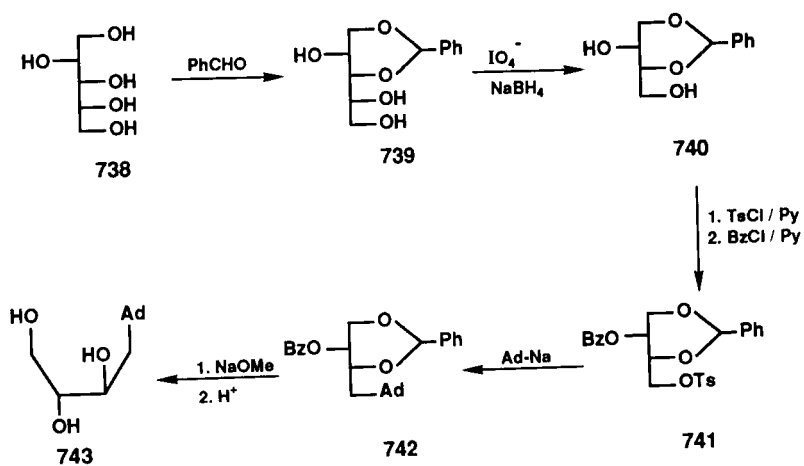
The synthesis of the enantiomeric *threo* analogs started from D- or L-arabinose (79CCCC593). Thus, the adenine analog **743** was prepared from D-arabinitol **738** by conversion to the benzyliene derivative **739**. Its periodate oxidation and reduction gave **740**, which was tosylated and then benzoylated to give **741**. Reaction of **741** with the sodium salt of adenine gave **742**, which was deprotected to give **743**.

The racemic DL-*threo* derivative **747** was prepared starting from ethyl DL-tartarate, whose reaction with dimethoxypropane gave **744**. Subsequent reactions, as shown in Scheme 144, gave **745**, then **746**, which was deprotected to **747**. An analogous synthetic procedure was also done for the preparation of the racemic erythro derivative (79CCCC593).

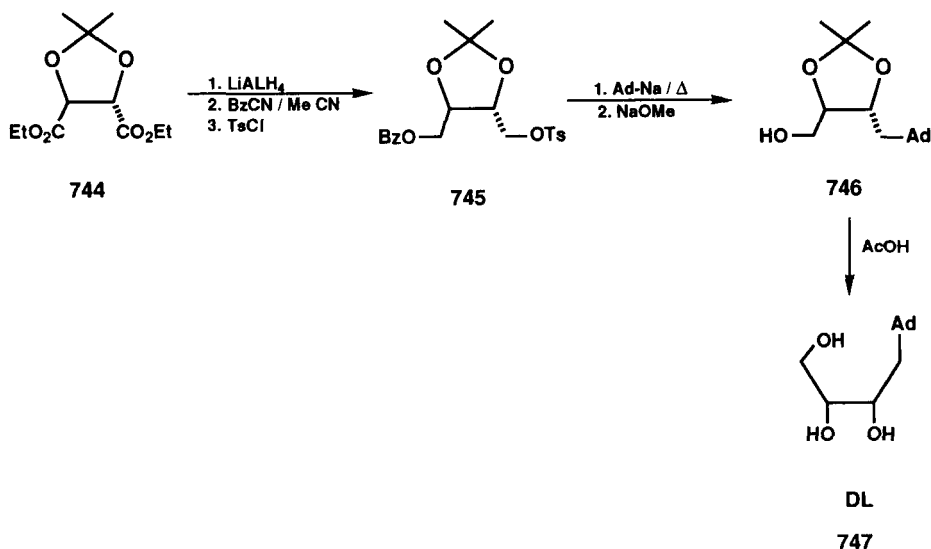
Eritadenine (**750**) is one of the significant hypo-cholesterolemic components of *Lentinus edodes* *sing*. Moreover, eritadenine and its stereomers have antiviral effects against vaccinia, vesicular stomatitis virus, and measles (85MI4). Several methods have already been elaborated for its synthesis. Thus, reaction of 4-amino-4-deoxy-D-erythronic acid (**748**) with 4-amino-6-chloro-5-nitropyrimidine followed by reduction of the nitro group gave **749**, whose cyclization with formamide gave **750** (69E1237). The condensation of 2(*R*),3(*R*)-*O*-protected dihydroxybutyrolactone **754** with the sodium



SCHEME 142

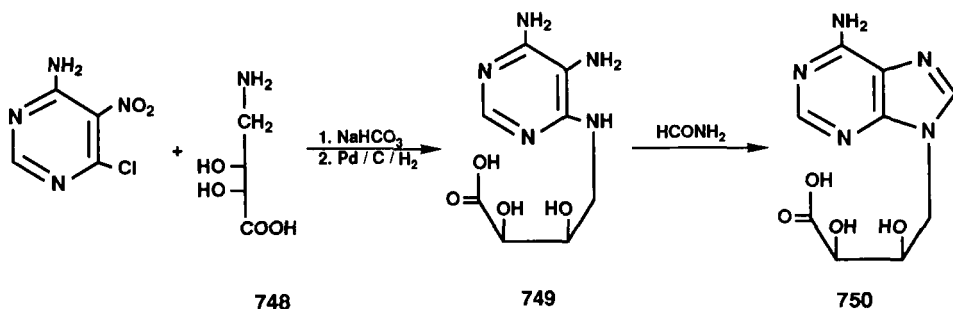


SCHEME 143

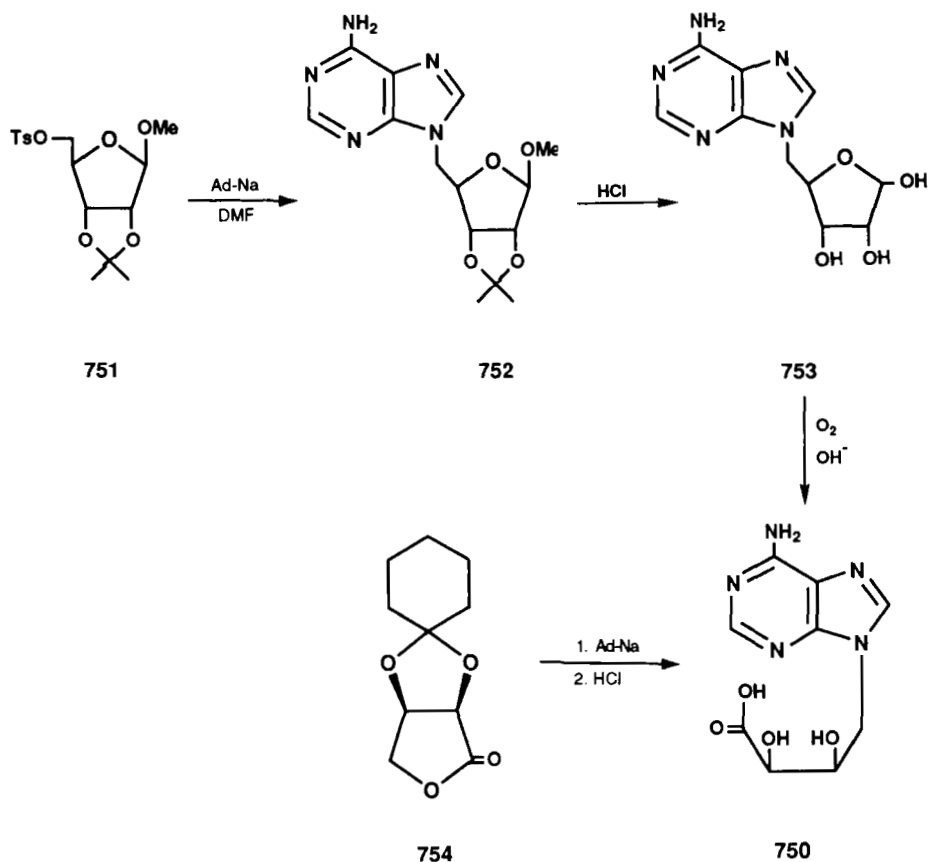


SCHEME 144

salt of adenine followed by hydrolysis gave **750** (71JOC1573). Alternatively, reaction of methyl-5-*O*-tosyl-2,3-*O*-isopropylidene- β -D-ribofuranoside (**751**) with the sodium salt of adenine gave the corresponding reversed nucleoside **752**, whose deprotection gave **753** and whose oxidation gave **750** (73JOC2887). This approach is convenient and was used successfully for the synthesis of analogs with different configurations and chain lengths [70JCS(CC)1047]. The enantiomeric and racemic forms were also prepared (84MIP1). The ethyl-4-(2-amino-6-chloropurin-9-yl)-2-hydroxybutyrate was prepared by alkylation with the 2-hydroxy-4-bromobutyrate ester (85USP4495190).

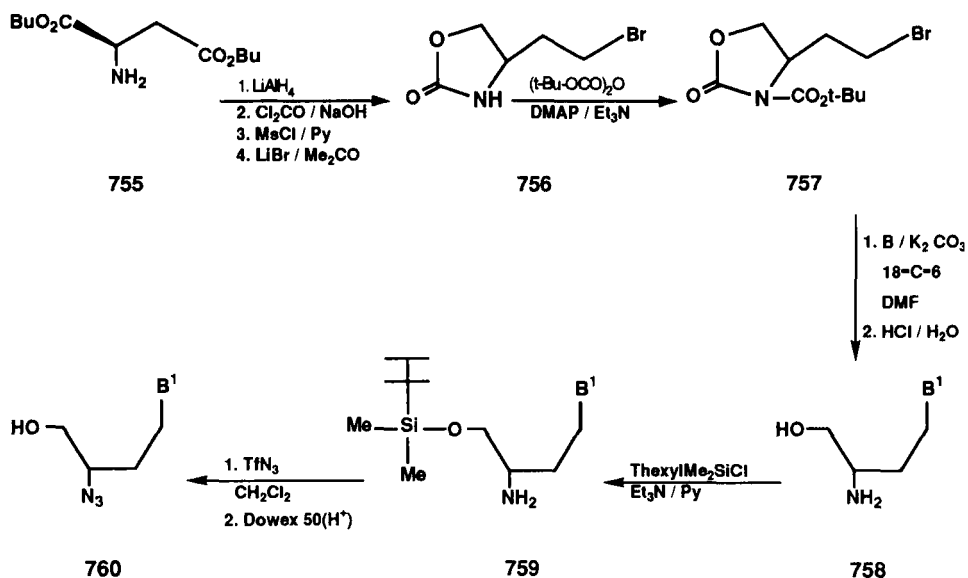


SCHEME 145



SCHEME 146

A modified analog of this type (**760**) was prepared from the di-*n*-butyl ester **755** of *R*(-)-aspartic acid, which was reduced to the diol and then to the oxazolidinone by reaction with phosgene, followed by mesylation and displacement of the mesylate group by bromide ion to give **756**, which subsequently was converted to the N-BOC **757**. Regioselective formation of the desired N-1 alkylated thymine derivative was achieved in three operations involving reaction of **757** with 4-methoxy-5-methyl-2-pyrimidinone in DMF/K₂CO₃, followed by opening of the oxazolidinone ring, N-BOC deprotection, and concomitant liberation of the C-4 amide carbonyl. Derivatives of the amino group of **758** were prepared by reaction of **758** with KOCN/H₂O, with H₂CO-HCO₂H or CNBr. The 3'-azido analogs **760** were prepared by reacting the *O*-protected amine **759** with



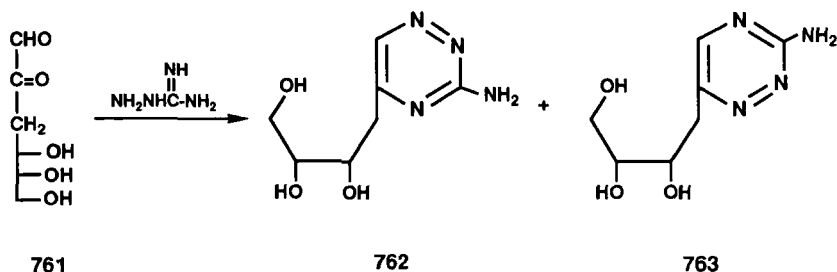
$\text{B} = 5\text{-Me-4-MeO-2-pyrimidinone}$, $\text{B}^1 = \text{Th}$

SCHEME 147

freshly prepared triflyl azide, followed by liberation of the 4'-hydroxyl group using DOWEX (90TL4879).

2. Acyclo-C-Nucleoside Analogs

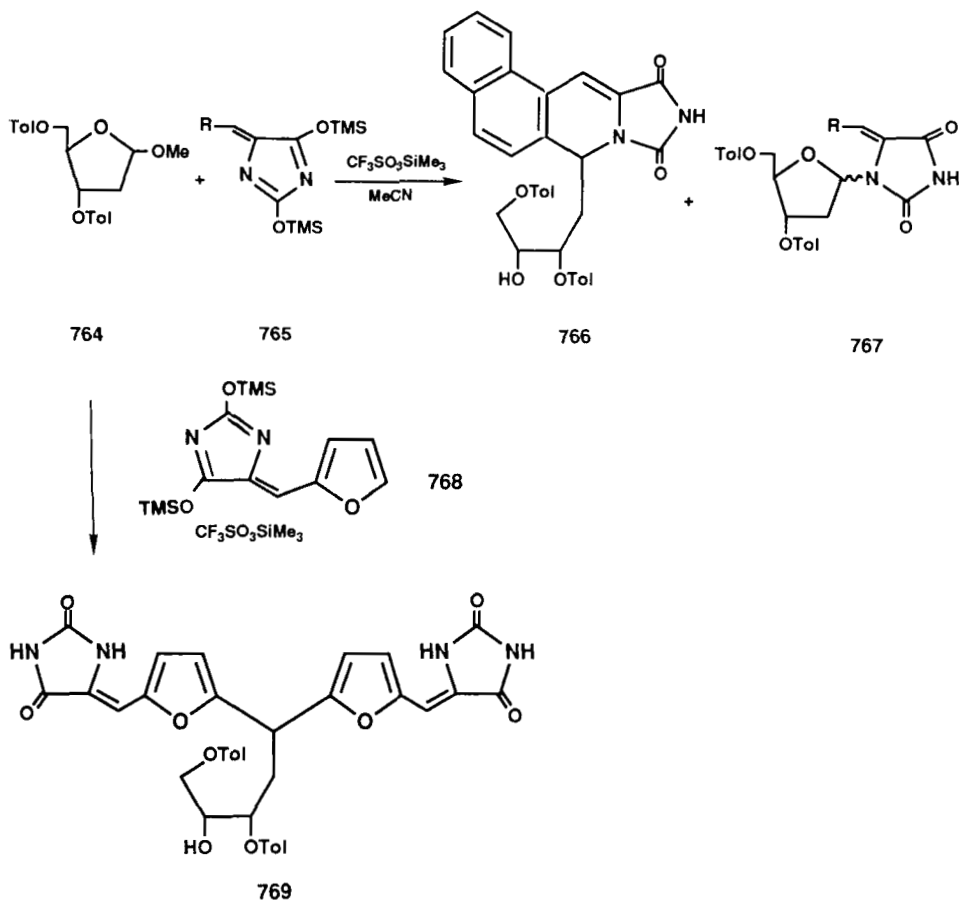
Reaction of 3-deoxyglucosulose **761** under physiological conditions with aminoguanidine gave a mixture of the two isomeric triazines **762** and **763** (92MI4).



SCHEME 148

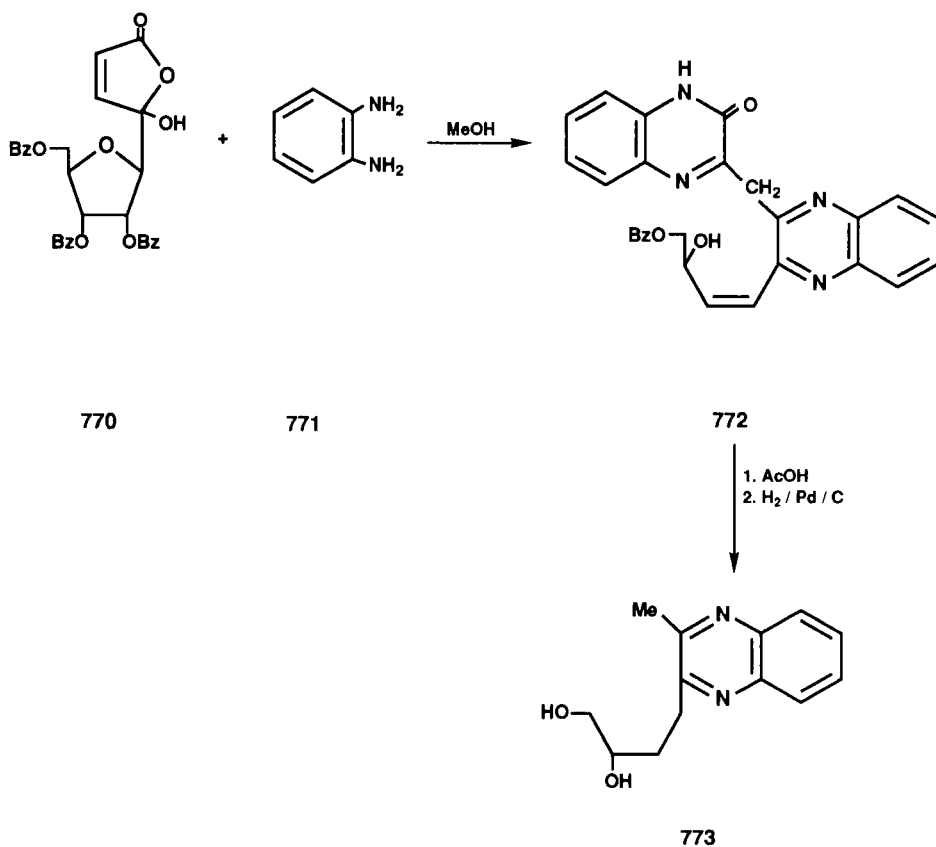
Reaction of methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranoside **764** with the trimethylsilyl derivatives of hydantoin **765** and **768** in presence of TMS triflate gave **766** and **769**, respectively (93JOC5994). The anticipated nucleoside **767** was formed in low yield in the former reaction. The formation of the acyclic analogs was accounted for by assuming the initial step to be a ring opening of the sugar to give an acyclic glycosyl cation.

Treatment of 1,2-diaminobenzene **771** with the furanone glycoside **770** in methanol gave the olefin **772**. Treatment of **772** with AcOH followed by catalytic hydrogenation produced 2-[4-*O*-benzoyl-(3*S*)-3-hydroxybutyl]-3-methylquinoxaline, whose debenzoylation gave **773** (93H2591).

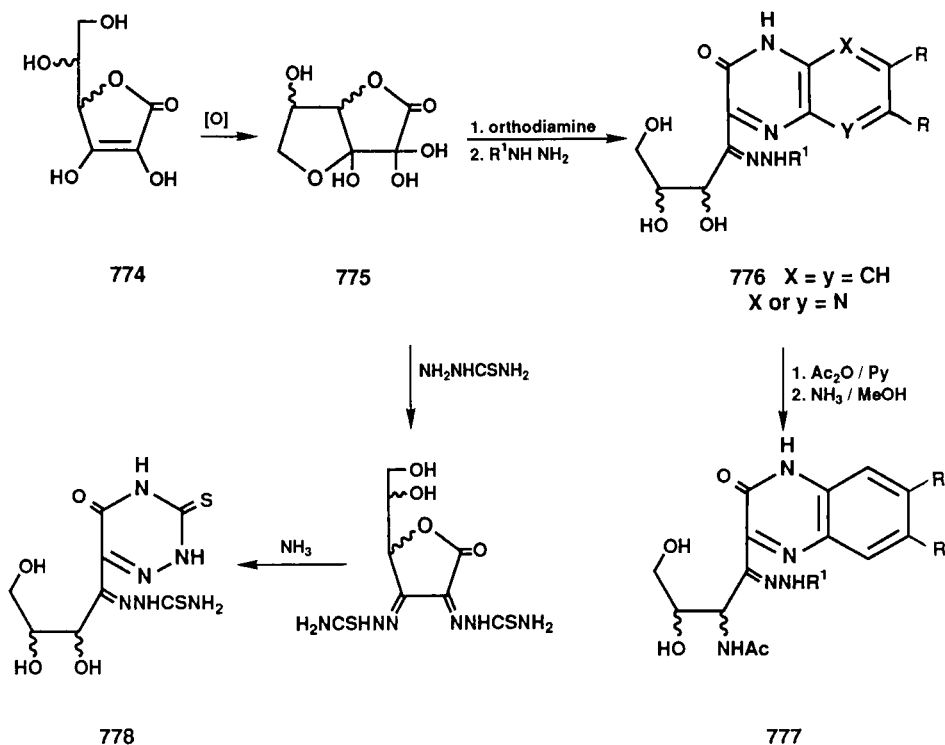


SCHEME 149

Oxidation of L-ascorbic acid and analogs generally formulated as **774** gave the dehydro derivatives **775**, whose reaction with 1,2-diaminobenzene or its derivatives were followed by reaction with different types of hydrazines to afford the quinoxaline derivatives **776** [78MI2, 78MI3, 78MI4, 78MI5; 82MI1; 86MI1; 88MI3; 90JCS(P1)2513]. The use of 2,3-diaminopyridine gave the two corresponding isomeric products (96UP3). However, reaction of **775** with thiosemicarbazide gave the respective bis(thiosemicarbazone); ring opening of the lactone followed by cyclization of the C-2 thiosemicarbazone residue with the C-1 generated carboxylic group gave **778** (92AHC233). Acetylation of **776** followed by deacetylation with methanolic ammonia gave **777** (92MI2).



SCHEME 150



SCHEME 151

ACKNOWLEDGMENTS

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1,3,2-Dioxathiolane Oxides: Epoxide Equivalents and Versatile Synthons

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I. Introduction

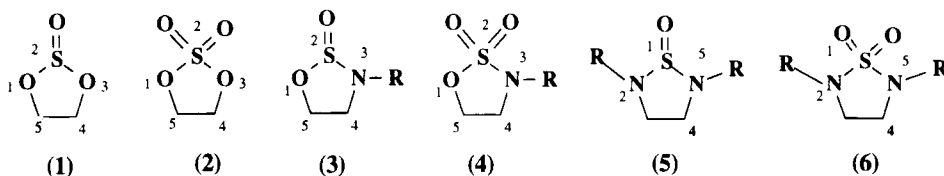
Since the first elegant approach to the synthesis of various 1,3,2-dioxathiolane 2,2-dioxides (cyclic sulfates) and their subsequent interesting stereochemical transformation by Gao and Sharpless (88JA7538), a number of research reports have appeared highlighting the usefulness of cyclic sulfates as very versatile synthons in organic synthesis. In the late 1980s, epoxides played a very vital role in organic synthesis (85MI2), presumably because of their high reactivity as well as simultaneous protection of adjacent functionalized carbon atoms from nucleophilic attack. They are usually superior to their acyclic counterpart because of their cyclic nature, which renders the competing elimination process stereochemically less favorable. In contrast, cyclic sulfates are superior to epoxides in their reactivity and their further ability to undergo a second nucleophilic displacement (pK_a 1.98, $R-O-SO_2O^-$) on the adjacent functionalized carbon atom.

The chemistry of cyclic sulfites and cyclic sulfates has been given much attention during recent years, especially after the publication of a review by the author (92S1035). This article presents a complete picture of the chemistry of cyclic sulfites and cyclic sulfates and thereby makes them a more extensive resource for further exploitation, especially in light of the availability of powerful tools with which to prepare nearly optically pure diols by an asymmetric dihydroxylation technique (92TA1317; 94CRV2483). Since the mid-1980s, epoxides have played a crucial role in organic synthesis (85MI2; 93MI1) because of their high reactivity. The cyclic sulfates have shared similar or even greater reactivity toward various nucleophiles. Although the chemistry of cyclic sulfites and cyclic sulfates has been known for a long time, their synthetic use has gained importance only recently. The parent ethylene cyclic sulfate has been known since 1932 (32JCS86), and extensive kinetic studies on the rate of hydrolysis have been reported (63JA602; 65JA3781; 70ACR145). Although the present chapter focuses on the chemistry of cyclic sulfites and cyclic sulfates, some chemistry of oxathiazole oxide and thiadiazole oxides is also described.

II. Nomenclature

The name cyclic sulfate originates from the sulfate ester of alcohols. Because in the present case the diol forms a part of the cyclic system, it is known as a cyclic sulfate. To avoid ambiguities, a systematic IUPAC nomenclature is required. Thus, the cyclic sulfite esters of 1,2-diols are named 1,3,2-dioxathiolane 2-oxides (**1**), and the corresponding cyclic sul-

fates 1,3,2-dioxathiolane 2,2-dioxides (2). Similarly, the sulfite ester of a 1,2-amino alcohol may be called a cyclic sulfamidite or 1,2,3-oxathiazole 2-oxide (3), and the sulfate ester a 1,2,3-oxathiazole 2,2-dioxide (cyclic sulfamidate, 4).



Similarly, cyclic sulfite and cyclic sulfate esters of the corresponding 1,2-diamines have been named 1,2,5-thiadiazole 1-oxide (5) and 1,2,5-thiadiazole 1,1-dioxide (6). In this chapter, emphasis is placed on cyclic sulfites and cyclic sulfates; however, the synthetic preparation and nucleophilic transformations of cyclic sulfamidites and cyclic sulfamidates are also compared.

III. Theoretical Aspects

Limited theoretical studies have been conducted. Some theoretical calculations support the conformational assignment of the molecule by other spectroscopic methods.

Calculations have been carried out to determine the conformations of ethylene sulfite and various substituted ethylene sulfites. The torsional angle ψ for ethylene sulfite was calculated using Buy's equation (68RTC1003) and was found to be $\psi = 44^\circ$.

Although it is not possible to calculate torsion angles of other substituted ethylene sulfites, it is possible to compare the coupling constant of vicinal protons for cis and trans conformers. The J_{vic} value for all the cis conformers of monosubstituted ethylene sulfite remains virtually unchanged; however, J_{vic} (trans) varies considerably, indicating a large change in torsion angle. The magnitude of the torsion angle for sulfites may be due to rapid interconversion of conformers [75JCS(P2)190] (see Fig. 1). Based on the coupling constant, the difference in the free energy between the two conformers (IIA and IIB) was estimated to be $0.2 \text{ kcal mol}^{-1}$ in favor of IIB and $1.3 \text{ kcal mol}^{-1}$ for III in favor of IIIB. This difference measures the interaction of the methyl group with an $\text{S}=\text{O}$ bond, i.e., $1.1 \text{ kcal mol}^{-1}$. The ΔG between II and III is ca. $0.90 \text{ kcal mol}^{-1}$.

A conformational study of 1,2,3-oxathiazole-2-oxide has been conducted using the semiempirical quantum-mechanical method PM-3 (89JCC209).

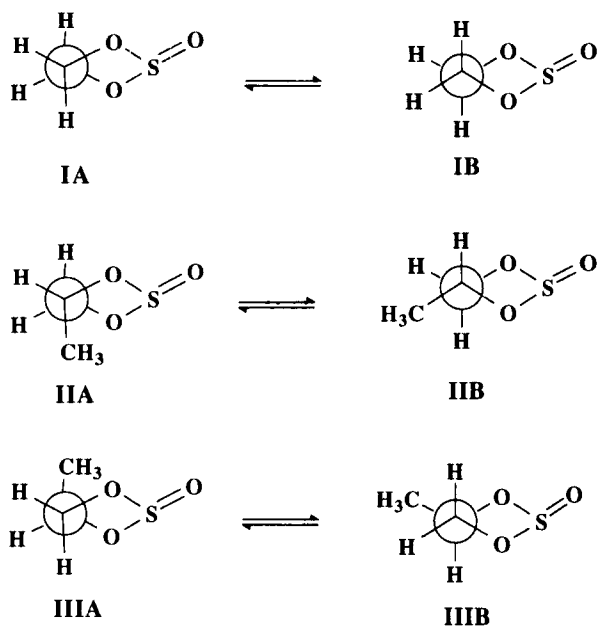


FIG. 1. Conformations of cyclic sulfites.

The potential energy surface (PES) for 3-phenyl-1,2,3-oxathiazolidine 2-oxide has been examined to locate the possible minimum energy structures. The dihedral angles related to distinct conformations of the five-membered ring and also to the torsion angles of the hydrogen and phenyl substituents were varied with the aim of locating all possible stationary points on the PES. Four minimum energy structures that may exist in equilibrium were located on the PES for 3-phenyl-1,2,3-oxathiazole 2-oxides. Analysis of these four structures shown in Fig. 2 (I–IV) shows that rotations of the phenyl substituents around the single bond in isomers II and IV are readily convertible to structures I and III. Thus, most likely there exist only two conformers (95JHC557), which are energetically very close.

In a separate study, *ab initio* calculations were carried out on sulfamic acid as a simple sulfamate model to test the effect of geometry change on pK_a (95JOC2003). The calculation showed that sulfamate with the ringlike geometry should be 3.6 pK_a units more acidic than acyclic sulfamate. This overall change was broken down into three factors affecting the pK_a . The N–S bond rotation accounted for a change of 0.22 unit, O–S bond rotation for 2.03 units, and a ring strain for 1.36 units.

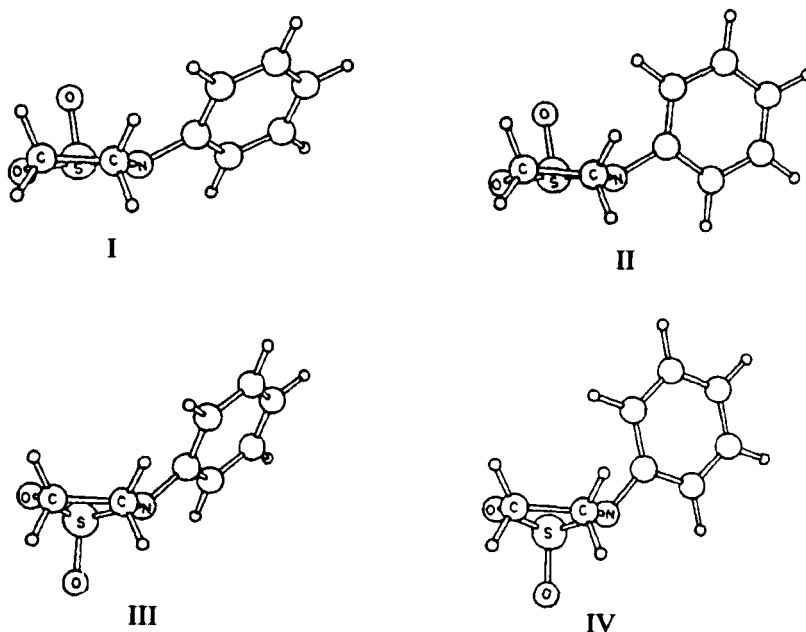
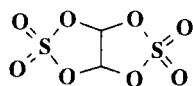


FIG. 2. The PM3 fully optimized conformers of the 3-phenyl-1,2,3-oxathiazolidine 2-oxide heterocyclic molecular system. (Reproduced with permission from *J. Heterocycl. Chem.*)

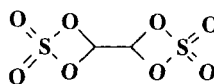
IV. Thermodynamic Aspects

A. DIPOLE MOMENT MEASUREMENT

The dipole moment of ethylene sulfate (**2**) was found to be 5.64 D in dioxane. Based on this, the dipole moment of glyoxal sulfate was calculated, and this led to the assignment of the structure as **7** and not **8**. The dipole moment of glyoxal sulfate **7** in dioxane was measured to be 5.35 D. Considering the dihedral angle between the two five-membered rings in **7** as 120°, one can calculate its dipole moment, which is in agreement with the measured value (68JHC289).



cis-glyoxal sulfate-(7)



(8)

The dipole moments of ethylene sulfite (**1**) ($\mu = 3.74$ D in benzene), ethylene sulfate (**2**) ($\mu = 5.64$ D in dioxane), and tetramethyl cyclic sulfate ($\mu = 6.05$ D in dioxane) have been measured. These measurements support the nonplanar ring structure of this class of compounds.

B. KINETICS AND MECHANISM OF HYDROLYSIS OF CYCLIC SULFITES

A considerable difference in the rate of hydrolysis of cyclic sulfites and that of their open counterparts or six-membered analogs has been observed. For example, cyclic *O*-phenylene sulfate hydrolyzes 2×10^7 times faster than diphenyl sulfate. Similarly, several cyclic sulfites have been hydrolyzed under acidic and basic conditions (60JCS201). The kinetic acceleration for both aliphatic and aromatic cyclic sulfites is ca. 10^3 times faster than that for their acyclic counterparts. In contrast, the rate of hydrolysis of ethylene sulfate is only 20 times faster than that of dimethyl sulfate (63JA602). Measurement of the heat of hydrolysis of *O*-phenylene sulfite and diphenyl sulfite indicates that they have a similar heat of hydrolysis, although *O*-phenylene sulfite hydrolyzes 10^3 times faster in an alkaline medium than diphenyl sulfite. The mechanism of hydrolysis of cyclic sulfite involves a two-step process. The initial rate-determining step is the attack of OH^- on sulfur, followed by rapid decomposition of the half ester [68JCS(B)1360]. The activation parameters have been measured; the difference in the reactivity of ethylene sulfite and dimethyl sulfite lies in the entropy of activation. With increasing ring size, the value of the activation parameter becomes almost identical to those of the open-chain sulfites. Thus, both open- and large-ring (>5 atoms) sulfites are mobile, and the ring system may twist and even flip. However, ethylene sulfite and *O*-phenylene sulfite are rigid structures. Thus, during alkaline hydrolysis, the molecules take a more orderly structure, leading to a loss of entropy and thus an increase in the free energy of activation. Hence, less energy is required for the hydrolysis of five-membered cyclic sulfites, which results in a much lower free energy of activation. Therefore, the enhanced reactivity of a five-membered cyclic sulfite is not due to ring strain. In fact, thermochemically, an absence of strain has been shown for a five-membered cyclic sulfite (62JA599).

V. Experimental Structural Methods

Various spectroscopic methods have been used to determine the structure and conformation of cyclic sulfites and cyclic sulfates.

A. IR SPECTROSCOPY

Organic sulfites give rise to medium or intense bands near 1210 cm^{-1} due to an S=O stretching vibration. In the case of ethylene sulfite, $\nu_{\text{S=O}}$ was found to be $1212\text{--}1216\text{ cm}^{-1}$ (neat). A pure and isomeric mixture of ethylene sulfite shows a solvent-dependent $\nu_{\text{S=O}}$ band (66TL4433). A number of cyclic sulfites have been studied at various concentrations. The range of $\nu_{\text{S=O}}$ for sulfites spans ca. 25 cm^{-1} , and with increasing polarity of the solvent, a decrease in wave number is noted. A dilution effect is also observed for all solvents and is positive, i.e., shifts to a higher wave number for the $\nu_{\text{S=O}}$ band [73JCS(P2)243, 73JCS(P2)1966].

B. ^1H NMR STUDIES

Several ^1H NMR studies have been conducted to assign the conformation of cyclic sulfites and cyclic sulfates [68JA715; 69JPC4020; 72CJC2370; 73JCS(P2)243, 73JCS(P2)1966]. Complex ^1H NMR spectra indicating a pyramidal sulfur atom have been obtained for ethylene sulfite (61JA2105). Chemical shift (δ ppm) and coupling constants (J , Hz) of some ethylene sulfites **9** are given in Table I to highlight the effects of substituents on the chemical shift and coupling constant [73JCS(P2)243, 73JCS(P2)1966].

The 100-MHz ^1H NMR spectra of several methyl- and phenyl-substituted ethylene sulfites have also been recorded and discussed in detail. The data were used to calculate the chemical shift difference between the ring protons by considering the shielding or deshielding effect. Thus, for ethylene sulfite, the chemical shifts of the protons cis (β) and trans (α) to the S=O bond were given by

$$\begin{aligned}\nu_{\beta} &= (\Delta\sigma_{\text{SO}})_{\beta} + \sum_0 \Delta\sigma_{\beta} \\ \nu_{\alpha} &= (\Delta\sigma_{\text{SO}})_{\alpha} + \sum_1 \Delta\sigma_{\alpha},\end{aligned}$$

where $(\Delta\sigma_{\text{SO}})_{\alpha,\beta}$ are specific contributions of the screening tensors at α and β due to the diamagnetic anisotropy of the S=O bond susceptibility, and $\sum \Delta\sigma_{\alpha}$ and $\sum \Delta\sigma_{\beta}$ are summations of several remaining average screening tensors that affect ν_{α} and ν_{β} . The calculation shows that within an error of 0.03 ppm, chemical shifts are in remarkably good approximation, and it confirms all assignments of proton sets. The chemical shifts in benzene relative to carbon tetrachloride solvent are greater for substituents trans to the S=O bond than for those substituents cis to the S=O bond. The average coupling constants of ethylene sulfite for geminal, cis vicinal, and

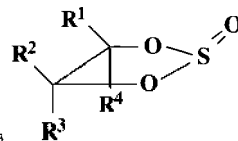
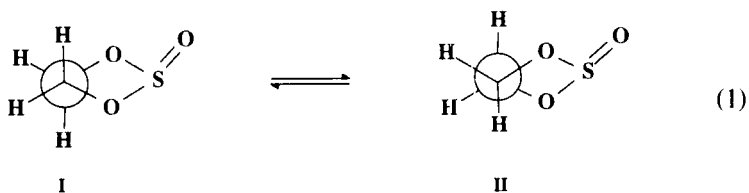


TABLE I
¹H NMR CHEMICAL SHIFTS (δ) OF CYCLIC SULFITE (9) IN CDCl₃

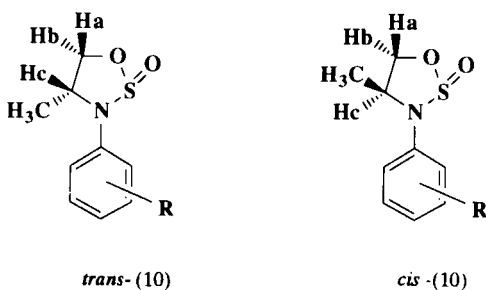
| S. no. | Compound | | | | Chemical shift | | | | Coupling constants (Hz) | | | | | |
|--------|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|-------------------------|-------|-------|-------|-------|-------|
| | R ¹ | R ² | R ³ | R ⁴ | R ¹ | R ² | R ³ | R ⁴ | 1,2 | 1,3 | 1,4 | 2,3 | 2,4 | 3,4 |
| 1 | H | H | H | H | 4.846 | R ¹ | 4.497 | R ³ | 6.88 | 6.70 | 2.3 | -8.42 | 1.3 | 1.2 |
| 2 | Me | H | H | Me | 1.667 | 4.428 | 4.167 | 1.351 | — | — | ±0.40 | -8.49 | ±0.56 | — |
| 3 | H | H | Me | H | 5.103 | 4.698 | 3.871 | 1.428 | 6.09 | 6.99 | 6.20 | -8.29 | — | — |
| 4 | H | Me | H | H | 4.568 | 4.220 | 4.462 | 1.594 | 9.09 | 6.07 | 6.23 | -8.56 | — | — |
| 5 | Me | H | Me | H | 4.100 | 4.635 | 1.447 | 1.535 | 8.87 | — | 6.14 | -6.13 | — | — |
| 6 | H | H | Me | Me | 5.002 | 1.297 | ≡R ² | ≡R ¹ | 6.42 | -0.15 | 5.71 | — | 1,3 | 1,2 |
| 7 | Me | Me | H | H | 4.662 | 1.514 | ≡R ² | ≡R ¹ | 6.64 | -0.15 | 5.86 | — | 1,3 | 1,2 |
| 8 | Me | H | Me | Me | 1.372 | 4.744 | 1.558 | 1.215 | 6.47 | — | — | — | — | ±0.45 |
| 9 | Me | Me | H | Me | 1.456 | 4.281 | 1.549 | 1.403 | 6.50 | — | — | — | — | ±0.44 |
| 10 | Me | Me | Me | Me | 1.539 | 1.324 | ≡R ² | ≡R ⁴ | 0.55 | — | — | — | — | 1,2 |
| 11 | H | H | H | Ph | 5.900 | 4.913 | 4.169 | 7.35 | 6.44 | 7.30 | — | -8.53 | — | — |
| 12 | Ph | H | H | H | 7.43 | 4.438 | 4.717 | 5.391 | — | — | — | -9.13 | 10.45 | 6.58 |
| 13 | Ph | H | Ph | H | 7.35 | 5.683 | R ¹ | 5.185 | — | — | — | — | 9.78 | — |
| 14 | H | H | Ph | Ph | 6.142 | ≡R ¹ | 7.04 | ≡R ³ | — | — | — | — | — | — |

trans vicinal protons are 8.27, 6.87, and 6.61 Hz, respectively. The effect of substitution in the ring shows a considerable change in the coupling constants, as shown in Table I.

From these studies, it has been concluded that ethylene sulfite exists in two twist-envelope forms that are interconvertible by rapid pseudo-rotation not involving inversion at the sulfur center [Eq. (1)].



Similar ^1H NMR studies of several substituted cyclic sulfamidites have been conducted to determine their conformations.



The ^1H NMR spectra of 3-aryl-4-methyl-1,2,3-oxathiazolidine 2-oxides **10** recorded at 400 MHz in CDCl_3 indicates that the ratio of cis and trans isomers depends on the nature of substituents on the aromatic ring (90JHC195) (Table II). From these studies it is clear that in 3-aryl-4-methyl-1,2,3-oxathiazolidine 2-oxide, the trans form, is predominant. The conformation of cis and trans forms also depends on the substituents.

For example, in a compound having the C-4-methyl cis to an $\text{S}=\text{O}$ bond, there will be a repulsive van der Waals interaction of 4.60 kJ mol^{-1} between a syn axial methyl group and the $\text{S}=\text{O}$ function and 1.26 kJ mol^{-1} for a CH_3 and O gauche interaction in I (Fig. 3). This results in a preferred gauche conformation of II. Similarly, conformers III and IV are interconvertible. In the case of the trans isomer, the preferred conformation is V or VI, in which the methyl group is equatorial and the hydrogen atom on C-4 is axial (Fig. 3). Lowe and Reed (90TA885) have carried out extensive NMR studies of sulfamidates and sulfamidites to assign the configuration at both sulfur and nitrogen. The configurational assignments of five- and six-

TABLE II
CHEMICAL SHIFTS OF PROTONS AND CARBONS IN CIS AND TRANS ISOMERS OF
3-ARYL-4-METHYL-1,2,3-OXATHIAZOLIDINE-2-OXIDE (10)

| R | Config. | ¹³ C Chemical shift | | | ¹ H NMR chemical shift | | | |
|--------------|---------|--------------------------------|----------------|------|-----------------------------------|----------|--------|----------|
| | | C ₄ | C ₅ | 4-Me | Ha (q) | Hb (q) | Hc (m) | 4-Me (d) |
| H | Cis | 55.5 | 75.8 | 15.8 | 4.77 | 4.79 | 4.24 | 1.41 |
| | Trans | 52.6 | 76.9 | 16.5 | 5.04 | 4.25 | 4.45 | 1.26 |
| <i>p</i> -Cl | Cis | 55.6 | 75.9 | 15.6 | 4.75 | 4.79 | 4.19 | 1.39 |
| | Trans | 52.8 | 77.0 | 16.3 | 5.03 | 4.25 | 4.39 | 1.24 |
| <i>p</i> -Me | Cis | 56.2 | 75.7 | 15.7 | 4.73 | 4.75 | 4.20 | 1.38 |
| | Trans | 52.8 | 77.2 | 16.2 | 5.00 | 4.19 | 4.41 | 1.24 |
| <i>O</i> -Cl | Cis | 58.6 | 75.67 | 16.7 | 4.66 (t) | 4.74 | 4.30 | 1.24 |
| | Trans | 54.3 | 77.1 | 15.4 | 4.97 | 4.16 (t) | 4.48 | 1.17 |
| <i>O</i> -Me | Cis | 61.3 | 75.5 | 16.4 | 4.69 | 4.71 | 4.02 | 1.25 |
| | Trans | 54.4 | 77.2 | 15.5 | 4.97 | 4.09 | 4.45 | 1.13 |

membered cyclic sulfamidite and sulamidates are shown in Fig. 4, along with their important ¹H NMR chemical shift values.

From the configurational analysis, it is apparent that when the sulfamidite is a part of a six-membered ring, a single diastereoisomer is formed with the S⁺—O[−] group in an axial position as shown in **12** and **13**. In contrast, when five-membered sulfamidites are prepared, both the epimers at sulfur are formed as shown in Fig. 4 (**11a** and **11b**; **14a** and **14b**).

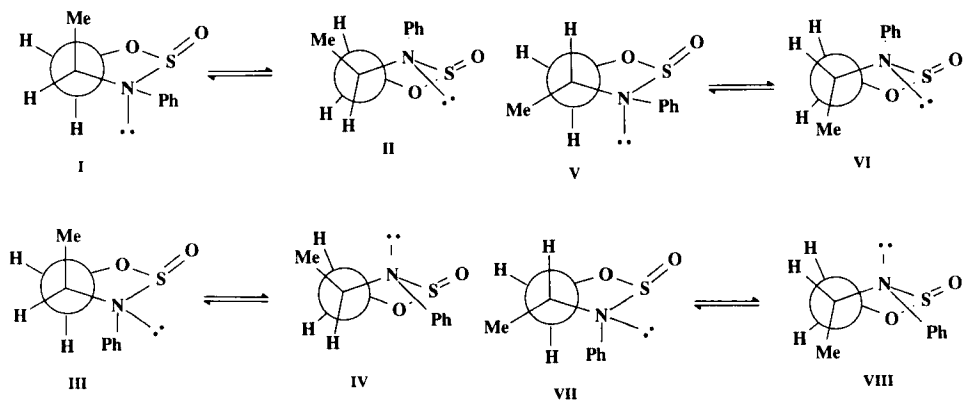


FIG. 3. Conformations of cyclic sulfamidite 10.

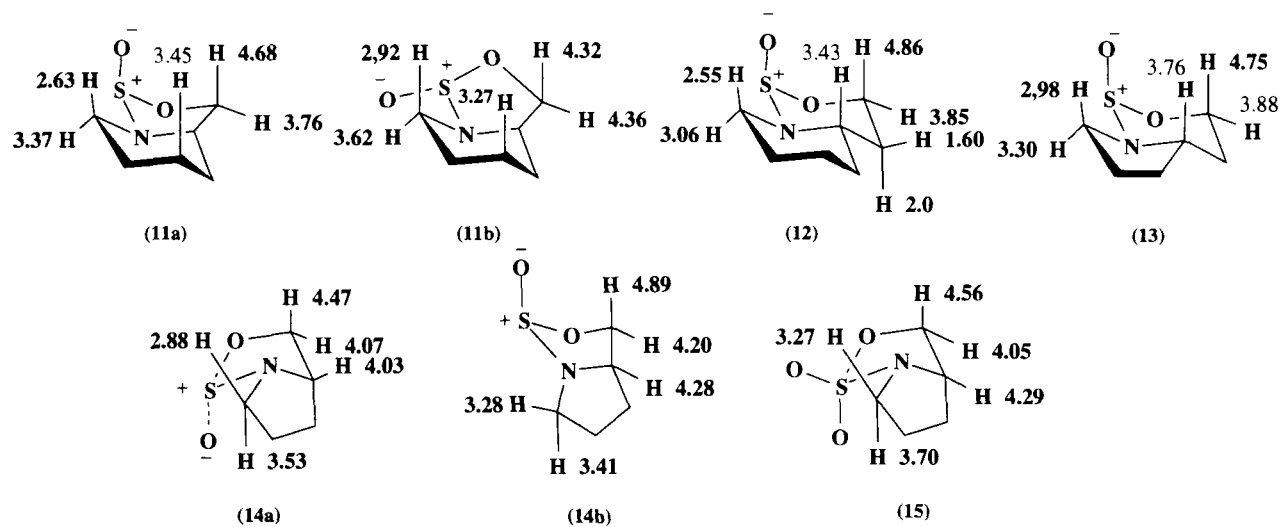


FIG. 4. ^1H NMR chemical shift of sulfamidites and sulfamidates.

C. ^{13}C NMR STUDIES

The ^{13}C NMR studies were conducted to determine the conformation of a cyclic sulfite and larger-ring cyclic sulfite esters (76CJC1428), since chemical shifts are highly sensitive to the stereochemistry of the $\text{S}=\text{O}$ bond. ^{13}C NMR data for various substituted ethylene sulfites are presented in Table III.

The chemical shifts shown in Table III are influenced by the substitution pattern and depend on the conformation of the ring. This study also supports the concept of twist envelope forms in which there is rapid pseudo-rotation not involving conformational inversion at the sulfur center. Similar studies were carried out on a six-membered cyclic ester; these have helped to distinguish between axial and equatorial substituents (76CJC1428). The ^{13}C NMR chemical shift values and conformational assignments are shown in Fig. 5.

Similarly, several substituted 3-aryl-1,2,3-oxathiazolidine 2-oxides (**10**) were examined by ^{13}C NMR (78BCJ323), and depending on the nature of the substituted aryl group, the chemical shifts of C_α and C_β carbons varied between δ 69.5–71.4 and 45.8–48.2, respectively.

D. ESR SPECTROSCOPY

Electron spin resonance (ESR) studies of various organic sulfites have been conducted. The radical was generated by an aqueous solution of

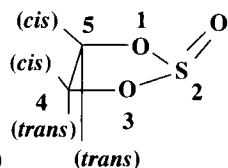
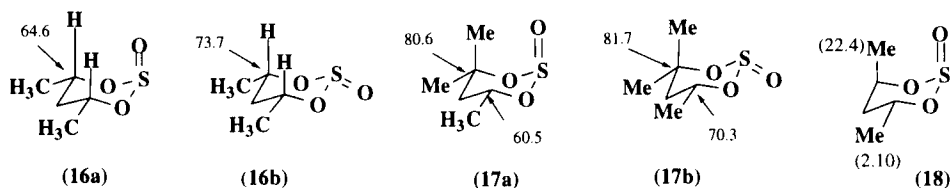


TABLE III

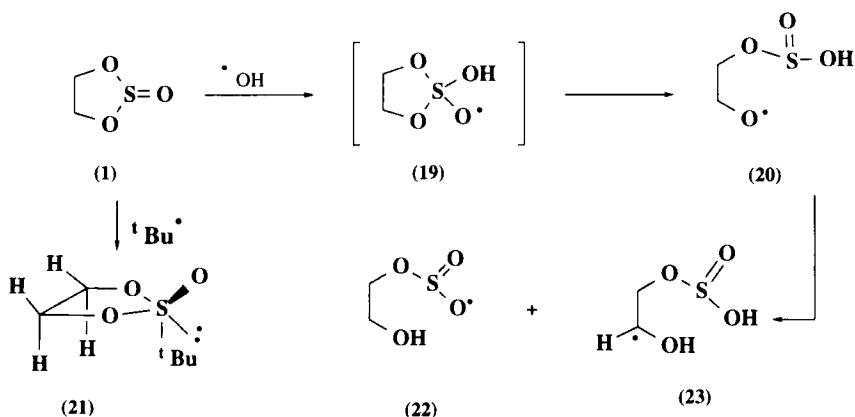
 ^{13}C NMR CHEMICAL SHIFTS (δ) OF ETHYLENE SULFITE (**9**) (IN CDCl_3)

| Compound no. | C_4 | C_5 | 4 Me (cis) | 4 Me (trans) | 5 Me (cis) | 5 Me (trans) |
|--------------|--------------|--------------|--------------|--------------|------------|--------------|
| 9-1 | 67.6 | 67.6 | — | — | — | — |
| 9-2 | 89.2 | 75.6 | 26.4 | 26.4 | — | — |
| 9-3 | 76.5 | 72.9 | R^1 | 17.8 | — | — |
| 9-4 | 80.2 | 70.9 | 18.7 | R^1 | — | — |
| 9-5 | 80.5 | 85.4 | 15.9 | — | 18.0 | — |
| 9-6 | 78.5 | 78.5 | — | 14.4 | — | 14.4 |
| 9-7 | 81.2 | 81.2 | 16.2 | — | 16.2 | — |
| 9-8 | 90.7 | 80.6 | 25.5 | 22.7 | — | 13.5 |
| 9-9 | 88.7 | 86.1 | 25.8 | 23.2 | 15.7 | — |
| 9-10 | 91.0 | 91.0 | 24.2 | 23.8 | 24.2 | 23.8 |

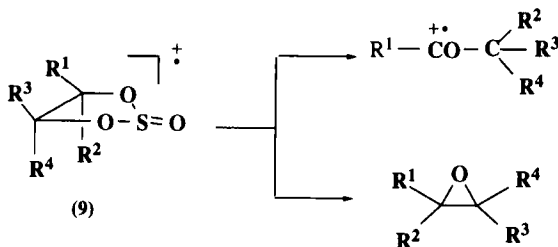
FIG. 5. ^{13}C chemical shifts (δ) of six-membered cyclic sulfites.

titanium(III) chloride, hydrogen peroxide, and ethylene sulfite in the cavity of an ESR spectrometer. The measurements were carried out at pH < 2 or at pH 9 where nitromethane was used to generate the nitro anion to trap the radical generated. Ethylene sulfite gave a singlet that was assigned on the basis of the g factor (2.0031) to $\text{SO}_3^{\cdot -}$. The spectrum with a (2H) 0.173, $a(2\text{H})$ 0.035 mT, g 2.003, is attributed to splitting of EtOSO_2^{\cdot} , which is likely to originate from $\text{HOCH}_2\text{CH}_2\text{OSO}_2^{\cdot}$ (**22**) as shown in Scheme 1. The first step involved the addition of the OH radical to the S=O bond to give **19**, which undergoes intramolecular H-atom abstraction by an alkoxy radical to form **22** and **23** via **20**.

Alternatively, the alkoxy radical **22** may abstract a proton from an $\alpha\text{-SO}_3^{\cdot -}$ to form **23**, which is trapped by $(\text{CH}_2\text{NO}_2)^{\cdot -}$. The radical **23** is suitable for fragmentation to form $\text{SO}_3^{\cdot -}$ [76JCS(P2)1040]. Similar studies were carried out in the presence of $^t\text{BuO}^{\cdot}$ radical, which shows the presence of sulfuranyloxy radical from ethylene sulfite having $g = 2.0044$, $a(1\text{H})$ 0.24, $a(2\text{H})$ 0.0037 mT [77JCR(S)173]. When di-*t*-butyl peroxide is photolyzed in the presence of ethylene sulfite in a solvent mixture of cyclopropane and ethyl-



SCHEME 1



SCHEME 2

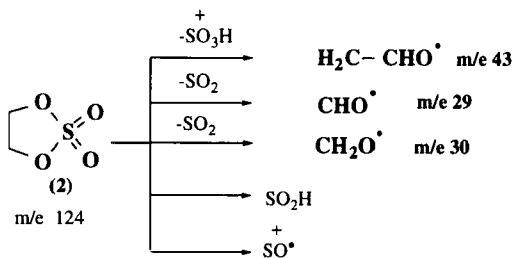
ene oxide (1:1), a spectrum of sulfuranyloxy radical is observed [a(1H) 2.38; a(2H) 0.37 G, g 2.0044 at 163 K]. The ESR spectrum of **21** shows a large unique proton splitting, which is probably from one of the quasi-apical methyleneoxy protons. The presence of a five-membered ring may increase the stability of **21** with respect to its acyclic analog (77JMR509).

E. MASS SPECTROSCOPY

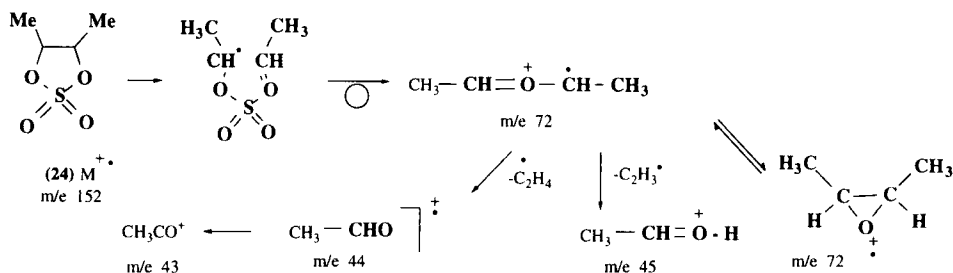
Lloyd and Porter have conducted extensive mass spectroscopic studies of several cyclic sulfites and cyclic sulfates of 1,2-diols, 1,3-diols, and 1,4-diols. One important fragment of a cyclic sulfite of a 1,2-diol is extruded SO_2 (77AJC569) (Scheme 2).

The mass spectrum of ethylene sulfate has little resemblance to that of ethylene sulfite. No significant loss of SO_3 was observed. The main fragments are small, simple organic ions along with ionized sulfur oxides and their protonated analogs (Scheme 3).

In the case of a substituted cyclic sulfate such as 4,5-dimethyl-1,3,2-dioxathiolane 2,2-dioxide (**24**), a fragment at m/e 72 and a metastable ion ($\text{M}^{++}-\text{SO}_3$) are formed. Further fragmentation of m/e 72 gives rise to m/e 43, 44, and 45. The fragments are depicted in Scheme 4.



SCHEME 3



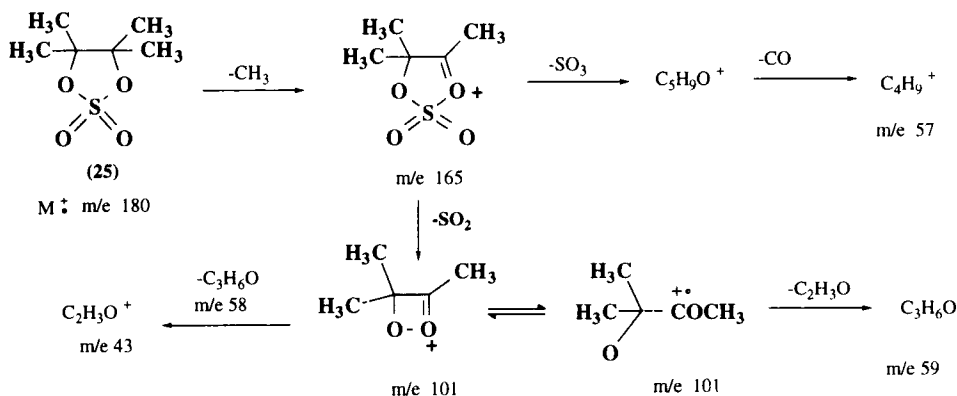
SCHEME 4

Increasing substitution by alkyl groups changes the fragmentation pattern. For example, the cyclic sulfate of 2,3-dimethylbutane-2,3-diol **25** did not lose SO₃; instead, it underwent a cleavage with the loss of a methyl group to give a (M⁺⁺–15) species. The fragmentation patterns are summarized in Scheme 5.

The cyclic sulfates derived from 1,3- and 1,4-diols showed a different fragmentation pattern. For example, sulfates of 1,3-diols fragment in an orderly manner via ($M-SO_3^+$), which are represented by oxetane radical cations, whereas 1,4-diol cyclic sulfates fragmented via tetrahydrofuran-like intermediates (77AJC569).

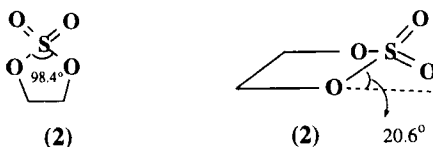
F. X-RAY ANALYSIS

The X-ray analysis of the parent ethylene sulfate indicates that the conformation of ethylene sulfate is puckered, with an angle of 20.6° between the



SCHEME 5

C₄ and the C₅ bond and an O—S—O bond angle of 98.4°, which is smaller than the tetrahedral angle of 109.5° (68JA2970). Hellier and Motevalli [95AX(C)129] have reported the X-ray structure of 4,5-dicyclohexyl-1,3,2-dioxathiolane 2-oxide as a monoclinic space group *p*21/*n*, with *a* = 11.0070 (10), *b* = 19.100 (3), *c* = 14.976 (2) Å, and β 110-21 (2)°, *Z* = 4, *dc* = 1.225, *dm* = 1.3, *R*(*F*²) = 0.0489, *RW*(*F*²) = 0.1153 for 3618 reflections. This clearly indicates that the cyclic sulfite adopts a half-chair (envelope) conformation with an S=O bond in a pseudo-axial position and a cyclohexyl group in a trans position.



VI. Structure Analysis

A. STRUCTURE ANALYSIS OF CYCLIC SULFITES AND CYCLIC SULFATES

From the preceding spectroscopic and physical constant measurements, the structures of cyclic sulfite esters have been analyzed. Electron diffraction studies suggest that a cyclic sulfite exists in a nearly planar form in the gaseous state (84CHEC851), whereas alkyl-substituted derivatives of a cyclic sulfite are in a puckered conformation. For example, the dihedral angles between O(3)C(4)—C(5)O(1); C(4)C(5)—O(1)S(2) and C(5)O(1)—S(2)O(3) have been found to be 41.2, 34.6, and 14.0°, respectively, suggesting the nonplanarity of the molecule. The S atom in a mono- or 4,5-disubstituted cyclic sulfite is asymmetric, and the S=O group possesses chiroptical properties. The CD spectra of *cis*-**26** and *trans*-**27** suggest a twist envelope conformation with an axially placed S=O group and an equatorially placed methyl group (74JOC2073).

The CNDO/2 calculation for the endo conformation suggests that the electron pairs of the ring oxygen atom are oriented at an angle of about 45° to each other. The steric rigidity of the molecule decreases the antibonding interaction in the *n_s*—*n_o* orbital and increases the antibonding interaction in the *n_o*—*π_{so}* orbitals. Thus, these two should have equal energies. The photoelectron spectra of cyclic sulfite (**1**) supports this, and the first band shows double intensity (72AGE436). The NMR studies (¹H, ¹³C, and ¹⁷O) support a twist envelope structure (*vide supra*), which undergoes pseudo-rotation without inversion of the S center, and therefore the *cis* and *trans* protons of ethylene sulfites are magnetically equivalent [84JCS(CC)466; 88MRC671]. Similarly, all protons of ethylene sulfate are magnetically

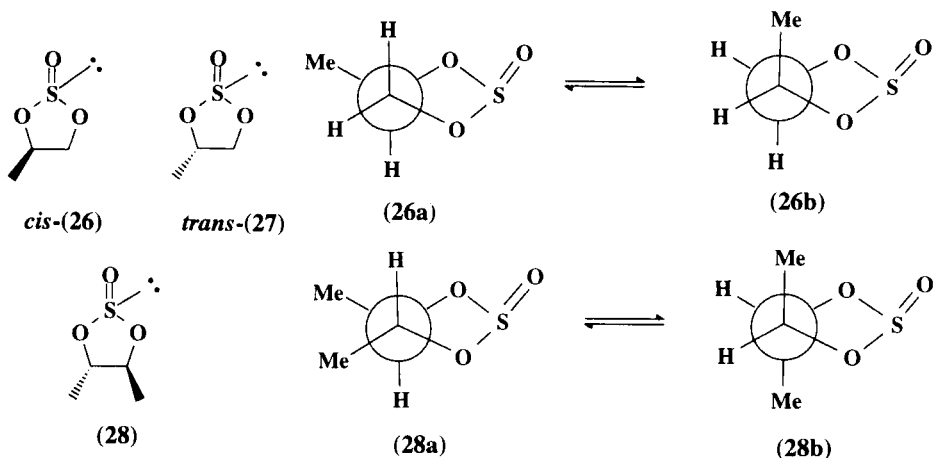
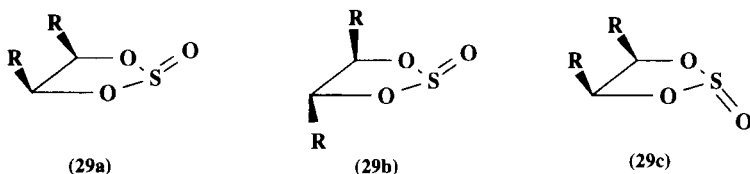
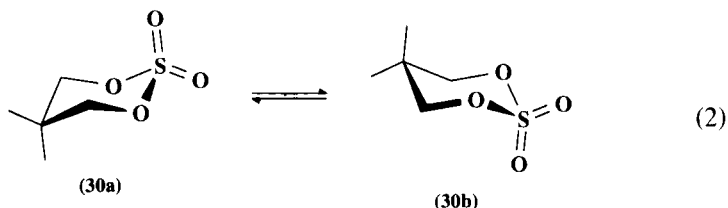


FIG. 6. Conformational structures of substituted cyclic sulfites.

equivalent. However, monosubstituted derivatives of a cyclic sulfite such as **26** and **27** show conformations having predominantly equatorial substituents. This is further supported by a dipole moment measurement (*vide supra*). Because of the position of the oxygen atom, a 4-substituted derivative exists in *cis* and *trans* forms, whereas a 4,5-disubstituted cyclic sulfite exists in three isomeric forms, viz **29a**, **29b**, and **29c**. Interestingly, *meso*- and *dl*-hydrobenzoin and 2,3-butanediol have been reported to give only one cyclic sulfite.



In contrast, a six-membered ring cyclic sulfate exists in a chair conformation [Eq. (2)]. Temperature-dependent NMR studies indicate an energy barrier of 8.1 ± 0.2 kcal mol⁻¹ for chair-chair interconversion. The high reactivity of a cyclic sulfate has been attributed to ring strain, although the origin of this ring strain is not clear.



It has been speculated that the possible cause of ring strain might be (a) angle strain, (b) partial double bond character between the ring oxygen and sulfur due to $2p(\text{O})-3d(\text{S})$ orbital interaction, or (c) 1,3-nonbonding interactions between the ring oxygen and the exocyclic oxygen (76PS1341).

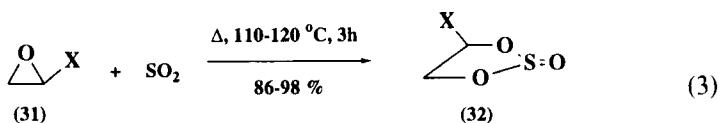
B. STRUCTURAL ANALYSIS OF CYCLIC SULFAMIDITES

Similar to that of a cyclic sulfite, the $\text{S}=\text{O}$ bond of cyclic sulfamidites has acetylenic anisotropy (61JA2105). For this reason, deshielding of oxathiazolidine ring substituents cis to the sulfoxide bond is observed (cf. Section V,B). The mean anisotropic effect of an $\text{S}=\text{O}$ bond between cis and trans protons at C_5 has been found to be 0.36 ppm. Using this value and the averaged chemical shift difference (0.8 ppm) between geminal protons H_a and H_b for trans compounds and the shielding effect of an adjacent (methyl) group, the H_a proton in a cis form can be expected to appear at higher field than the H_b proton in **10**. From ^{13}C NMR, the average chemical shifts of cis and trans C_4 and C_5 carbon appeared at δ 60.0 and 54.0 (see Sections V,B and V,C).

VII. Synthesis of Cyclic Sulfites and Cyclic Sulfates

A. SYNTHESIS OF CYCLIC SULFITES

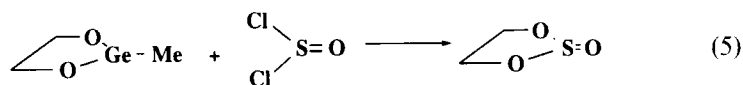
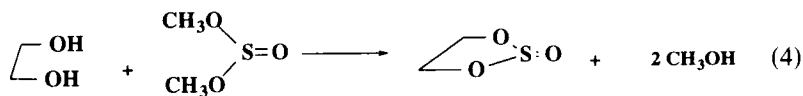
The commercial synthesis of ethylene sulfite is carried out by the reaction of ethylene oxide and sulfur dioxide at room temperature in the presence of a tertiary amine (51USP2798877; 52BRP670159; 89EUP324691) or Lewis acid (93MI4, 93MMC2605). A polymer is formed initially and is heated to provide ethylene sulfite in quantitative yield. By a similar strategy, 4-methyl-, 4-chloromethyl-, and 4-hydroxymethyl-1,3,2-dioxathiolane 2-oxides were prepared from the corresponding epoxide and sulfur dioxide in the presence of a catalytic amount of tetramethylammonium bromide at 110–120°C (61JGU1230) in high yield [Eq. (3)]. An inorganic salt is also used as a catalyst for copolymerization of ethylene oxide and SO_2 (93MI3). Similarly, a Lewis base can be used as a catalyst (93MMC2605).



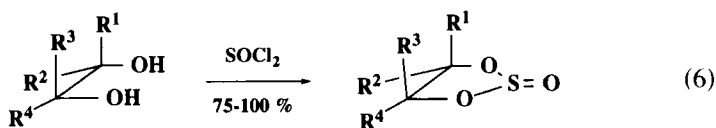
Cyclic sulfites of medicinal and biological relevance and industrial importance have been prepared by the reaction of glycidols with various alkoxides, followed by dehydrochlorination of the resulting diols with thionyl chloride [81JAP(K)81/152461; 82JAP(K)57/169463; 83JAP(K)58/103349; 87JAP(K)62/36372; 89EUP298399; 90EUP343053, 90EUP399899].

Several substituted cyclic sulfites have been prepared by the reaction of glycidol with a suitable *sec*-amine to furnish an amino diol, which is then treated with thionyl chloride in the presence of a base such as pyridine or triethylamine. This strategy of preparation of cyclic sulfites is of commercial importance because amine-substituted cyclic sulfites have been used as intermediates in the pharmaceutical industry (82JAP(K)82/02246; 84JAP(K)59/07186; 85MIP2; 86JAP(K)61/227578).

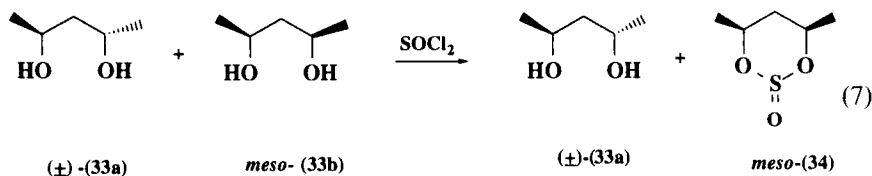
Glycerol furnished 4-chloromethyl-1,3,2-dioxathiolane 2-oxide, whereas *dl*-erythritol and *D*-mannitol gave the corresponding bis and tris(cyclic sulfite) (26MI1; 31CB1142). Thus, many monoprotected glycerols and substituted 1,2-propanediols were converted into cyclic sulfites with thionyl chloride (58JOC2013). 4-Vinylethylene sulfite was prepared by alcoholysis of dimethyl sulfite with erythrol (47JA2955). Similarly, ethylene sulfite can also be obtained by transesterification of ethylene glycol with dimethyl sulfite (67TL901; 76CRV747) [Eq. (4)]. More recently, such an exchange reaction has been observed with several germylated heterocycles with thionyl chloride to give cyclic sulfites (89MI3) [Eq. (5)].



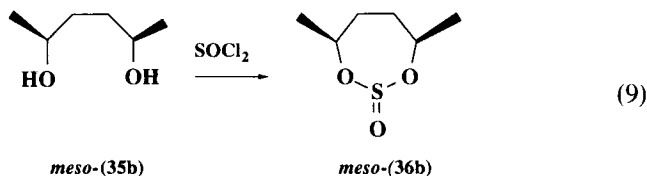
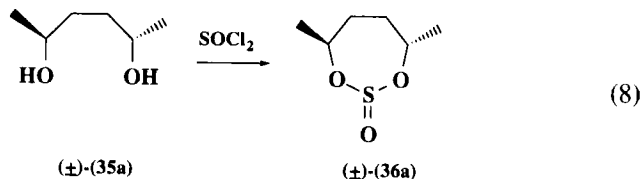
Several cyclic sulfites have also been prepared by the reaction of the corresponding glycols with sulfur tetrafluoride (87ZOR1111; 88ZOR1633). However, the most convenient method of preparing ethylene sulfite is by the reaction of ethylene glycol and thionyl chloride (66HC1) [Eq. (6)]. The use of dichloromethane led to an improved yield of product (50JA5497). Several optically active substituted cyclic sulfites have been prepared using optically active diols with thionyl chloride in the presence or absence of a suitable base [91JCS(CC)95]. The presence of a suitable base is required for substrates carrying acid-labile substituents to scavenge the hydrogen chloride generated in the reaction [73JOC3510; 89TL655; 95IJC(B)1023] or for unstable cyclic sulfites that might undergo subsequent reaction with hydrogen chloride (95JOC5983).



A preparation of a cyclic sulfite under controlled conditions has been used to resolve *meso*- and *dl*-2,4-pentanediols and 2,5-hexanediols. In the absence of any base or catalyst, *meso*-2,4-pentanediol reacts with thionyl chloride faster than *dl*-diol, and (\pm)-diols can be recovered in 27.5% yield (94TA657) [Eq. (7)].



In contrast, *dl*- and *meso*-2,5-hexanediols react with SOCl_2 to give *meso*- and *dl*-cyclic sulfites, respectively [Eqs. (8) and (9)].



In addition, there are other methods of synthesis of cyclic sulfites. A number of cyclic sulfites that have a wide range of application in medicine, chemistry, and industry have been prepared. Some of the cyclic sulfites are summarized in Table IV [for typical procedure, see 89TL3659; 91JCS(CC)95; 92S1035].

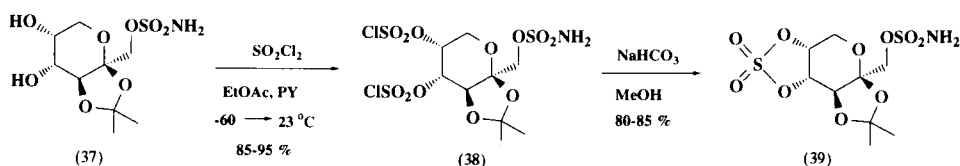
B. SYNTHESIS OF CYCLIC SULFATES

Synthesis of the cyclic sulfates has been summarized in a recent review (92S1035). In this section, only salient features are highlighted.

Unlike the commercial synthesis of a cyclic sulfite from ethylene glycol and thionyl chloride or ethylene oxide and sulfur dioxide, the synthesis of the corresponding cyclic sulfite with sulfonyl chloride or sulfur trioxide gave a very poor yield of ethylene sulfate (59CJC1412; 60CJC1122; 61JA2105). However, a very good yield of the cyclic sulfite **39** by the reaction of sulfonyl chloride with sugar-derived glycol **37** in the presence of pyridine in ethyl acetate has been reported (93BMC2653) (Scheme 6).

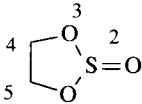
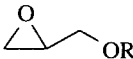
The first general method of synthesizing a cyclic sulfite by the oxidation of a cyclic sulfite was reported by Garner and Lucas (50JA5497) using calcium permanganate; however, this method gave only a moderate yield of the product (60JCS201). Later, Lowe *et al.* [83JCS(CC)266, 83JCS(CC)1392; 84JCS(CC)466; 90TA885] reported the use of ruthenium tetroxide, generated *in situ* from ruthenium dioxide and sodium periodate, for the oxidation of cyclic sulfite to cyclic sulfate under very mild conditions. The oxidation of cyclic sulfite to sulfate proceeds with retention of configuration at the S center as shown by ^{17}O -labeled studies [83JCS(CC)1392]. Using this method, several cyclic sulfates have been prepared in good yield (72–90%). The 1,3-cyclic sulfate of a bicyclic system was prepared by the oxidation of the corresponding cyclic sulfite using a stoichiometric amount of ruthenium tetroxide (81JOC3144) in 72% yield. However, the use of a stoichiometric amount of RuO_4 for the oxidation of a cyclic sulfite to a cyclic sulfate rendered this method synthetically unviable. This difficulty was surmounted by using a catalytic amount of RuO_4 in the presence of sodium hypochlorite as the secondary oxygen-transferring agent (89CL1689, 89EUP322521; 90USP4960904). However, the use of sodium hypochlorite led to the formation of some undesirable side products. Electrochemical oxidation of a cyclic sulfite to a cyclic sulfate has been achieved (93USP5271812). Using aqueous acidic (H_2SO_4) potassium permanganate in dichloromethane as an oxidizing agent, a moderate yield (35–61%) of cyclic sulfate has been obtained (90JOC1211).

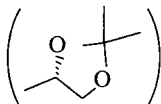
An alternative source for preparing a cyclic sulfate has been an epoxide. Thus, substituted epoxides have been converted into cyclic sulfates in quantitative yield with H_2SO_4 (78CL913). In lieu of H_2SO_4 , fluorosulfonic acid can also be used, which reacts with the epoxide to give a fluorosulfate that



SCHEME 6

TABLE IV
CYCLIC SULFITES (1,3,2-DIOXATHIOLANE-2-OXIDE) (9)

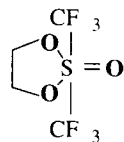
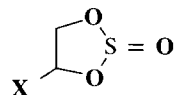
| Substituents | Substrates | Yield (%) | mp/bp (°C)/ torr [α] _D | References |
|--|---|-----------|---|----------------------------------|
|  4-ROCH ₂ - | HO-CH ₂ -CH ₂ -OH | 90 | 70/20 | 92S1035 |
| 4-ROCH ₂ - 4,5-(1,3,2-Dioxathiolan-4-yl-2-oxide) |  Glycerol derivatives D-Mannitol | 8–29 | 220–228/3.5 | 31CB1142, 58JOC2013, 61JGU1230 |
| 4,5-Dimethyl | 2,3-Butanediol | 78–91 | 60/10 | 61JA2105 |
| 4,4,5,5-Tetramethyl | Pinacol | 55 | 44–45 | |
| 4,5-Diphenyl | Hydrobenzoin | 100 | 129–131 | 54JA1211, 72JOC2589, 91JCS(CC)95 |
| 4,4,5,5-Tetraphenyl | Benzopinacol | 38 | 137–138 | 72JOC2589 |
| 4-Ph | Phenylethane-1,2-diol | 98 | | 89TL2623, 91JCS(CC)95 |
| 4,5-(CO ₂ R) ₂ | Dialkyl tartrate | 84–90 | | 91JCS(CC)95 |
| 4,5-(CH ₂ COOR) ₂ | Dimethyl 3,4-dihydroxy adipate | 60 | | 53BSF540, 55BSF1241 |
| 4-Alkyl | Substituted 1,2-diol | 48–85 | | 58JOC2013, 61JGU1230, 90JOC1211 |
| 1,3/1,4-Cyclic sulfite | 1,3/1,4-Diols | 25–80 | | 90JOC1211 |
| 4,4,5,5-Tetrafluoro | 1,1,2,2-Tetrafluoroethane-1,2-diol | | | 86BSF891 |
| 4-Cyclohexyl | 2-Cyclohexylethanol | 95 | | 89TL2623 |
| 4,5-bis | 1,2:5,6-Diisopropylidene-D-mannitol | | | 89TL655 |



4-C₆H₅-5-PO(OEt)₂
 4-(*p*-MeO-C₆H₄);5-COOEt
 4,5-Dicycloalkyl

4,4-Diphenyl
 4-Phenyl-5-methyl
 4-Vinyl
 4-Vinyl-5-methyl
 4-Styryl
 4-Phenyl

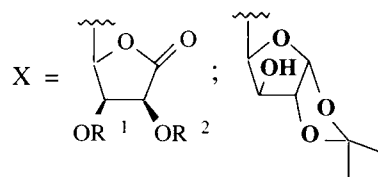
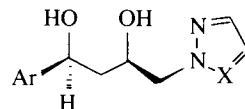
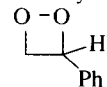
4-CH₂-N₂;
 5-Aryl



PhCHOHCHOHPO(OEt)₂
p-MeO-C₆H₄-CH(OH)COOEt
 1,2-Dicycloalkyldiol

Ph₂CHOHCH₂OH

CH₂=CH-CHOH-CH₂OH
 CH₂=CH-CHOH-CH(Me)OH
 4-Phenyl-3-en-1,2-diol



90 [α]_D = +36.8 95IJC(B)1023
 98 [α]_D = -113.3 95JOC5983
 15-78 53BSF737, 59LA(627)1,
 60JCS201
 74 90SL479
 94ACS183
 90SL224
 90SL331
 48-60 93TL3667
 92JA5591

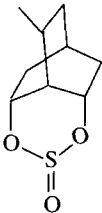
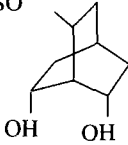
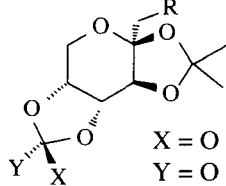
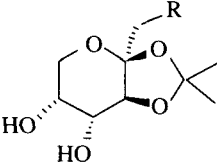
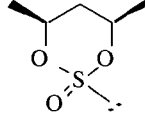
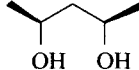
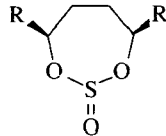
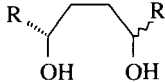
16-40 87JMC1054

89MI1, 93EUP552651

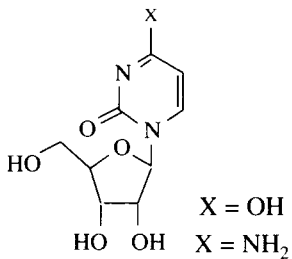
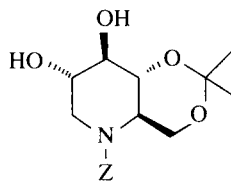
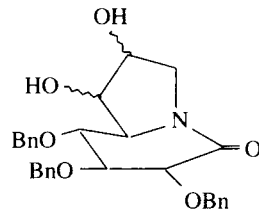
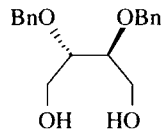
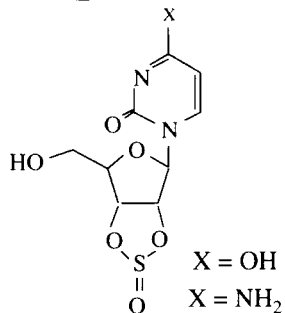
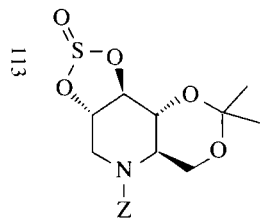
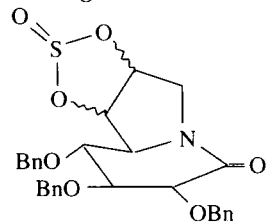
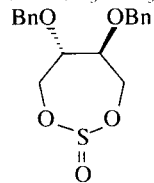
57 93IC3205

(continues)

TABLE IV (Continued)

| Substituents | Substrates | Yield (%) | mp/bp (°C)/ torr [α] _D | References |
|--|---|-----------|---|------------|
| TBSO | TBSO | 94 | | 81JOC3144 |
|  |  | | | |
|  |  | 100 57 | 151–153 197–199 | 93BMC2653 |
| <p>X = O ; Y = lone pair - exo</p> <p>Y = O ; X = lone pair - endo</p> | <p>When R = SO₂NH₂ exo:endo = 5.3:1</p> <p>When R = CH₂C₆H₅ exo:endo = 1.6:1</p> | | | |
|  |  | | | 94TA657 |
| <p>meso -</p>  | <p>meso-</p>  <p>(±) or meso</p> | | | 94TA657 |

R = CH₃ or C₅H₁₁ (±) or *meso*



90

95BSF829

96TL547

99

90MI1

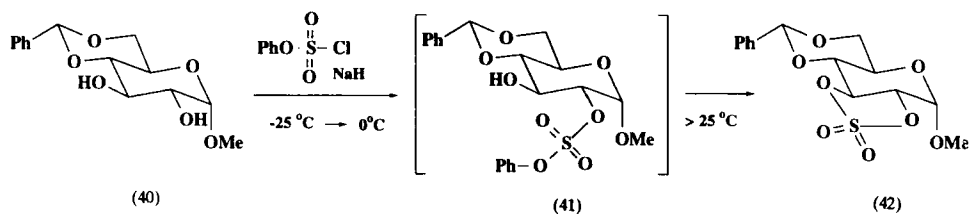
81

253-254

75BCJ505

85

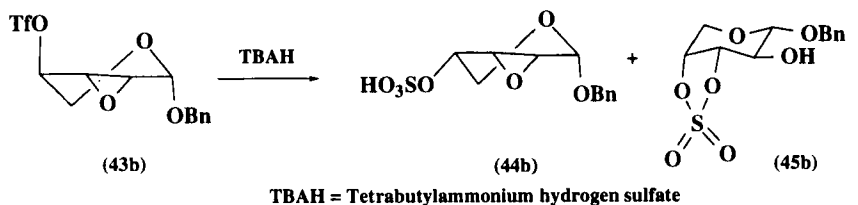
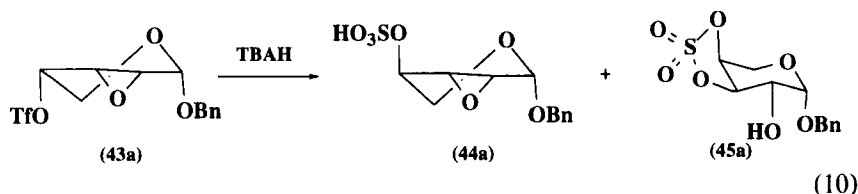
104-105



SCHEME 7

readily cyclizes in the presence of a base to give the corresponding cyclic sulfate (85TL6405). Cyclic sulfate has also been prepared by the reaction of dianions of diols with *N,N*-sulfuryldiimidazole in the presence of a strong base such as sodium hydride (85MI3). A few less common methods for the preparation of cyclic sulfates have been reported for a properly substituted glucopyranoside. For example, in the presence of NaH, phenyl chlorosulfate reacts with methyl 4,6-*O*-benzylidene- α -D-glucopyranoside (40) to give 2-phenyl sulfate 41 at -25 to 0°C , which upon warming to room temperature and above ($>25^{\circ}\text{C}$) led to the formation of 2,3-cyclic sulfate 42 by participation of the 3-OH group [89(190)39] (Scheme 7).

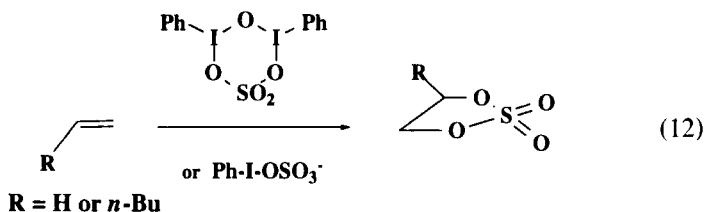
An interesting rearrangement of 2,3-anhydropyranoside 4-triflate to cyclic sulfate has been observed by treatment with tetrabutylammonium hydrogen sulfate [90JCS(P1)1573] [Eqs. (10) and (11)].



TBAH = Tetrabutylammonium hydrogen sulfate

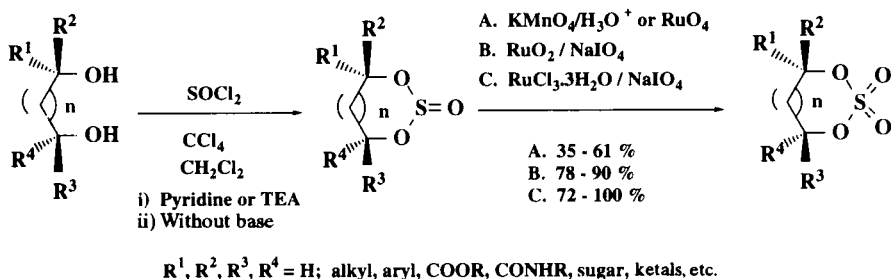
Olefins can directly be functionalized to cyclic sulfates using a hypervalent iodine reagent (86TL3971, 86ZOR450) [Eq. (12)].

From the foregoing, it is clear that the difficulties associated with the preparation of cyclic sulfates account for their rare use in mainstream

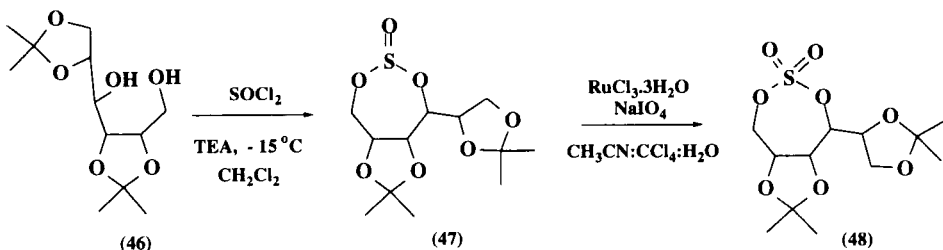


synthetic organic chemistry, until recently, when a catalytic method for the oxidation of cyclic sulfite using RuCl_3 with NaIO_4 was reported by Sharpless (88JA7538; 89MIP1). This is the most general method of synthesis of cyclic sulfates (72–100%). A number of cyclic sulfates have been synthesized with this method. A few representative examples of cyclic sulfates are listed in Table V. Different synthetic procedures are summarized in Scheme 8.

With this method, six- and seven-membered cyclic sulfates have also been prepared from the corresponding 1,3- and 1,4-diols. For example, Van Boom prepared seven-membered cyclic sulfate **48** from 2,3:5,6-diisopropylidene-D-mannitol (**46**) using $\text{SOCl}_2/\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$ followed by oxidation of the corresponding sulfite (**47**) by $\text{RuCl}_3 \cdot 3\text{H}_2\text{O} - \text{NaIO}_4$ (89TL5477) (Scheme 9) (for experimental procedure, see 88JA7538).

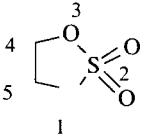
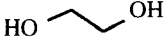

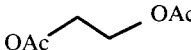
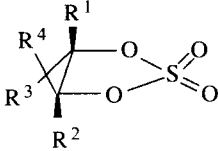
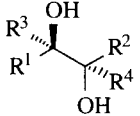


SCHEME 8



SCHEME 9

TABLE V
CYCLIC SULFITES (1,3,2-DIOXATHIOLANE 2,2-DIOXIDE)

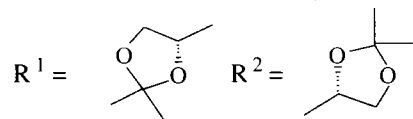
| Substituents | Substrates | Yield (%) | mp/bp (°C)/torr [α] _D | References |
|--|---|------------------|---|---|
|  <p>1</p> |    | <p>48 23</p> | <p>99</p> | <p>68JHC289, 76CJC1428, 95T5169 48BSF1002, 60JCS201</p> |
| 4,5-Dimethyl | 2,3-Butanediol | 45–54 | | 50JA5497, 61BSF1495 |
| 4,5-(ClCH ₂ –CHCl) ₂ | D-Mannitol | 60 | | 93BCJ513 |
| 4,4,5,5-Tetramethyl | 2,3-Dimethylbutane-2,3-diol | 21 | 105 | 59CJC1412 |
|  |  | <p>36–52</p> | <p>131 (dec)</p> | <p>74JOC3415</p> |
| R ¹ = R ² = COOR | R ³ -R ⁴ = H (2 <i>R</i> ,3 <i>R</i>) | 63–91 | | 88JA7538 |
| R ¹ = alkyl, R ² = H | 1,2-Alkanediol | 92–97 | | 89TL2623, 90SL479 |
| R ¹ = R ² = 4,5-dialkyl | <i>sym</i> -Diol | 89–97 | | 88JA7538 |
| R ¹ = alkyl, R ² = COOR | 2,3-Dihydroxy ester | 89–97 | | 88JA7538 |
| R ¹ = H, R ² = CONHCH ₂ Ph | <i>N</i> -Benzyl-2,3-dihydroxy glycidamide | 64 | 95–97 | 88JA7538 |
| R ¹ = R ² = R ³ = H, R ⁴ = SiMe ₃ | | 73 | | 94JCS(P1)1061 |
| R ¹ = R ² = dialkyl, R ³ = H, R ⁴ = SiMe ₃ | | | | |
| R ¹ = R ² = alkyl, aryl, or H | (2 <i>R</i> ,3 <i>R</i>)-Diol | 75–90 | | 88JA7538 |
| R ¹ = <i>n</i> -C ₁₂ H ₂₅ , R ² = CH ₂ CH ₂ OR | | 91 | | 92JOC6344 |

$R^1 = \text{CH}_2\text{OR}$, $R^2 = \text{H}$

$R^1 = \text{CHMe}_2$, $R^2 = \text{H}$

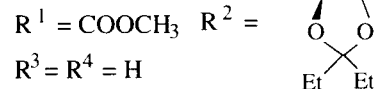
$R^1 = \text{CH}_2\text{-CHCNAr}$, $R^2 = \text{H}$

$R^1 = \text{Ph}$, $R^2 = \text{COOR}$ ($R = \text{Me}$)
($R = \text{Et}$)



$R^3 = R^4 = \text{H}$

$R^1 = R^2 = R^3 = \text{H}$; $R^4 = \text{CH}_2\text{OTBS}$
 $-\text{H}_2\text{C}$



$R^3 = R^4 = \text{H}$

$R^1 = \text{CH}_2\text{Ph}$; $R^2 = \text{PO}(\text{OMe})_2$

$R^1 = R^3 = R^4 = \text{H}$; $R^2 = -\text{C}(\text{CH}_3)_2-\text{CH}=\text{CH}_2$

4-(PhCHR-), $R = \text{F}$, $R = \text{OMe}$,
 $R = \text{Me}$

(RR)- or (SS)-4,5-Diphenyl

4,5(R,R)-Bis(3'-benzyloxy-4'-methoxy)phenyl

(S)- or (R)-4-Phenyl

(R)- or (S)-4-Ethyl

(R)- or (S)-4-Methyl

(R)- or (S)-Ph-CHF

1,2:5,6-Diisopropylidene-D-mannitol

84-93

60

98

94

87

95

65

68

75

79

77

50

61

—

124-126

$[\alpha] = -51$

62/1

50/1

73JOC3510, 89TL655,
93JOC3767, 90SL479
94JOC2179

95TL2725

92SL723

94JCS(CC)21

95IJC(B)471

89TL655

89TL655

89TL655

94JOC7930

95TL4595

89CL1689

88JA7538, 89TL2623

90TL7591, 91TL1775

88JA7538

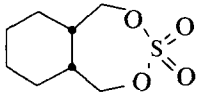
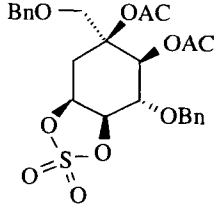
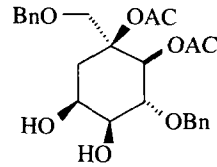
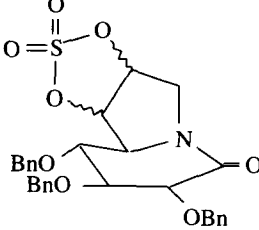
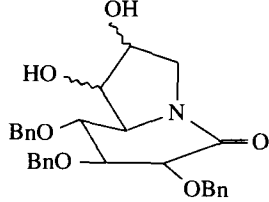
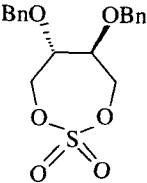
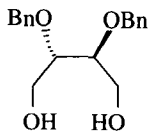
90JOC1211

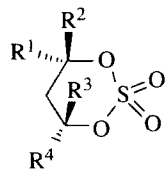
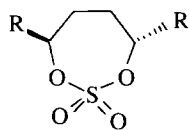
90JOC1211

89CL1689

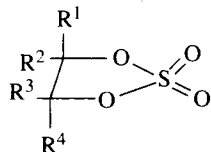
(continues)

TABLE V (Continued)

| Substituents | Substrates | Yield (%) | mp/bp (°C)/torr $[\alpha]_D$ | References |
|---|---|-----------|------------------------------|------------|
|  | | 89 | 58–59 | 95TA3055 |
|  |  | 74 | 61–67 | 95AGE1643 |
|  |  | 55 | | 96TL547 |
|  |  | 96 | $[\alpha]_D = +94$ | 95BSF829 |

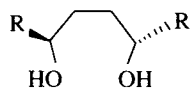


$R^1 = R^2 = R^3 = R^4 = H$
 $R^1 = Me, R^2 = R^3 = R^4 = H$
 $R^1 = R^2 = R^3 = H; R^4 = Me$
 $R^1 = R^3 = H; R^2 = R^4 = CH_3$

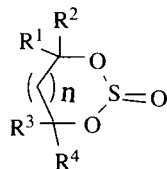


$R^1 = H, Me, CF_3; R^2 = H, Me$
 $R^3 = COOEt, CONH_2, H; F; R^4 = COOEt, F$
 $R^1 = H, NF_2, R^4 = NF_2,$

$R^3 = H, alkyl, R^2 = alkyl$
 $R^1 = R^2 = R^3 = R^4 = Me$



$R = Me, R = Et, R = i-Pr$
 $R = n-C_5H_{11}, c-C_6H_{13}$



77-78

 $[\alpha]_D = +19.9$

90TL3637, 95JA4423
91JA8518

83JCS(CC)266,
83JCS(CC)1392
84JCS(CC)466, 90TA885

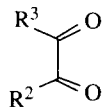
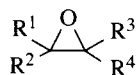
87

90JOC1211

90

90

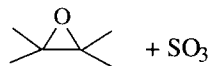
78



41-53

78CL913, 85TL6405

65CB2248

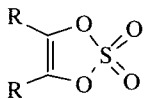
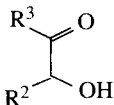
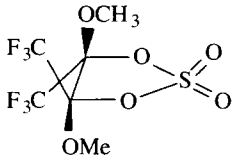
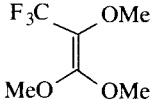
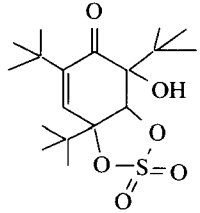
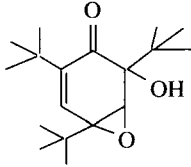
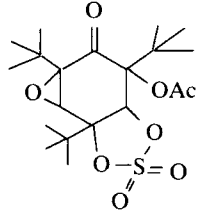
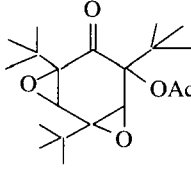


90

92FRP2664274

(continues)

TABLE V (Continued)

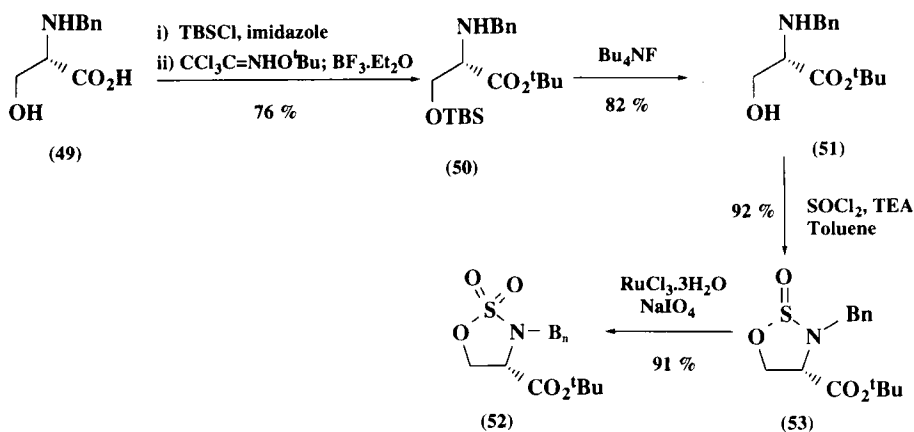
| Substituents | Substrates | Yield (%) | mp/bp (°C)/torr [α] _D | References |
|--|--|-----------|---|----------------------|
|  R = Ph; Mes |  + SOCl ₂ | 5 | 157–159 | 63JOC1075 |
|  |  | | | 77JA1214 |
|  |  | 24 100 | 19–20 112–113 | 90IZV2048 78CL913 |
|  |  | | 153–155 | 78CL913 |

C. SYNTHESIS OF CYCLIC SULFAMIDITES AND CYCLIC SULFAMIDATES

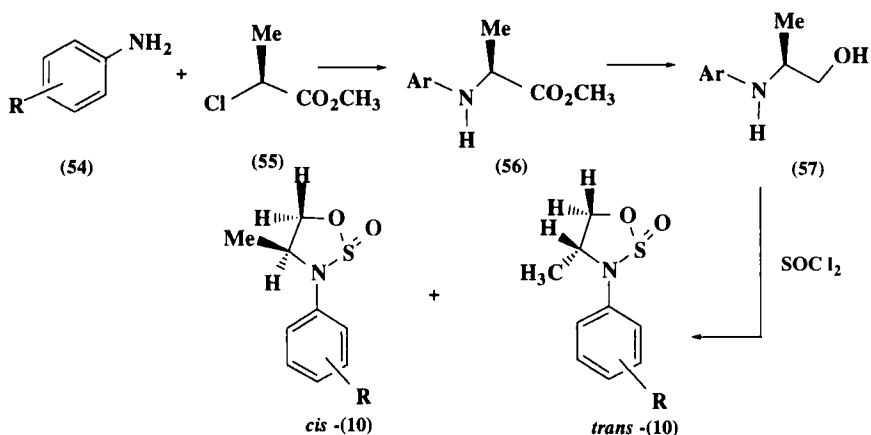
Cyclic sulfamidites and cyclic sulfamidates have been prepared from L-serine. L-Serine was first converted into L-serine-*O*-sulfate in 40% yield, which was then converted into 1,2,3-oxathiazolidine-4-carboxylate 2,2-dioxide (67BCJ1554) in poor yield. Later, Baldwin *et al.* (90TA881) reported an excellent overall yield of cyclic sulfamidate (**52**) derived from L-serine (**49**), as shown in Scheme 10.

Yamada *et al.* (82JHC1553; 90JHC195) have prepared several cyclic sulfamidites by reacting the corresponding anilines and methyl α -chloropropionate, followed by LAH reduction and further reaction of the amino alcohols **57** with thionyl chloride, to furnish a mixture (trans: cis = 1.13 to 2.57) of stereoisomers of cyclic sulfamidite **10** (Scheme 11). The trans isomer was always formed preferentially. Similarly, different amino acids were reduced to the corresponding amino alcohols, which were converted into cyclic sulfamidites using thionyl chloride (90TA877; 91JOC3177; 95JMC810, 95TA1667). Cyclic sulfamidites were oxidized to cyclic sulfamidates using $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}/\text{NaIO}_4$ (91JOC3177).

Several syntheses of cyclic sulfamidites are known (65JOC2763; 68BCJ1925; 69JOC175; 73JA6349; 75JOC949). Prolinol was converted into bicyclic sulfamidite **60** and sulfamidate **59** (90TA877, 90TA885) (Scheme 12) and ephedrine into a mixture of diastereomeric 3,4-dimethyl-5-phenyl-1,2,3-oxathiazolidine 2-oxide (73JA6349; 91TL5885). Similarly, Lowe *et al.* prepared cyclic sulfamidite analogs of penicillanic acid [89JCS(CC)1702; 90TA885].



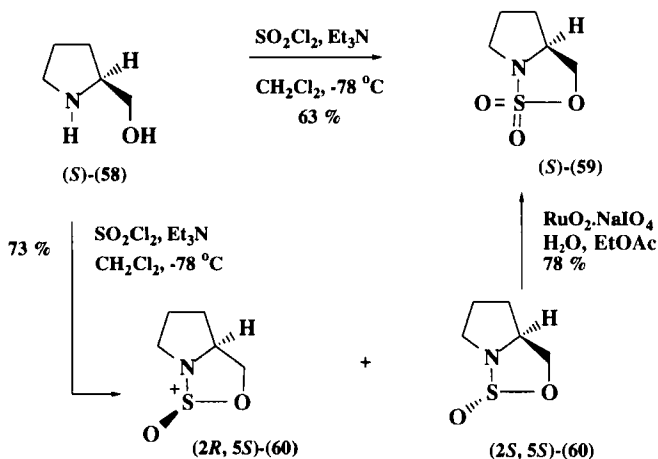
SCHEME 10



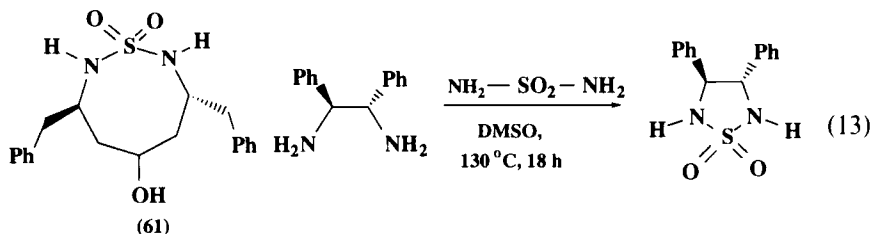
SCHEME 11

D. SYNTHESIS OF CYCLIC SULFAMIDES

Although this class of compounds is not the main subject of this chapter, a few examples have been cited for comparison. Unlike other analogs of cyclic sulfate esters, cyclic sulfamides can be prepared by the reaction of 1,2-diamines with sulfamide itself (92TL6661) [Eq. (13)]. Eight-membered cyclic sulfamide (61) has been used as an HIV-protease inhibitor (95TL6383; for a general procedure for the preparation of cyclic sulfamidites and cyclic sulfamidates, see 90TA877).

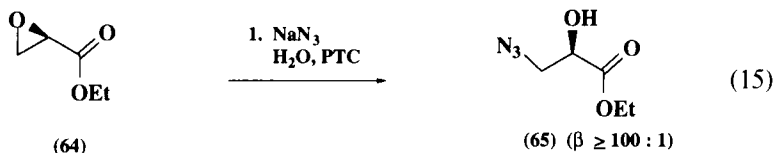
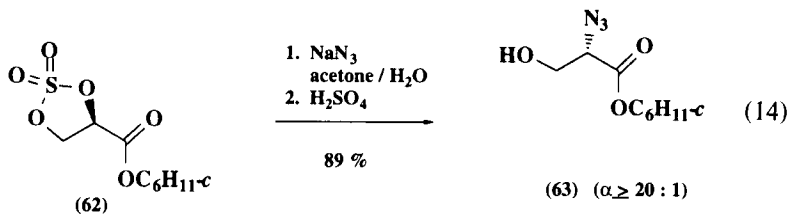


SCHEME 12



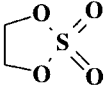

VIII. Reactivity

The reactivity of cyclic sulfates and epoxides toward nucleophiles is similar. In contrast, the reactivity of a cyclic sulfite is poorer than that of cyclic sulfates or epoxides. However, with good nucleophiles, cyclic sulfites can react well at relatively higher temperature. The regio- and chemoselectivity of cyclic sulfites and sulfates toward nucleophiles is different from that of epoxides. For example, cyclic sulfate **62** reacts with sodium azide in acetone–water to give preferentially α -azidoester **63** ($\alpha/\beta \geq 20:1$), whereas the epoxy ester **64** gives exclusively the β -substituted product **65** ($\beta:\alpha \geq 100:1$) [Eqs. (14) and (15)].



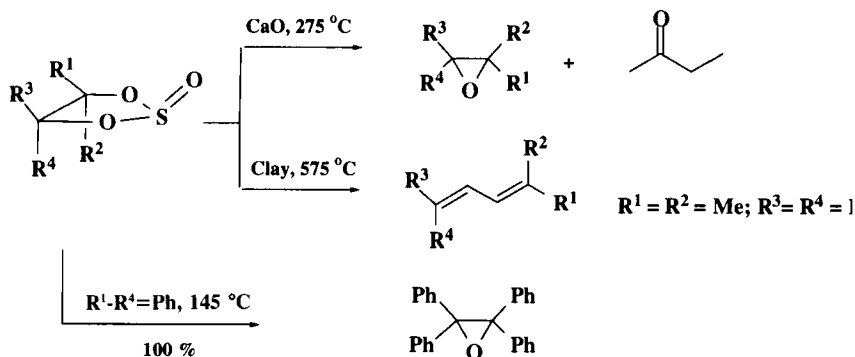
A comparison of ethylene cyclic sulfate and ethylene epoxide is shown in Table VI. In some cases, the reactivities of cyclic sulfates and epoxides are complementary to each other. At present, using Sharpless asymmetric dihydroxylation (92TA1317; 94CRV2483), which furnishes nearly optically pure diols in many cases, it is possible to prepare stereochemically pure cyclic sulfates. It is becoming possible to prepare cis and trans epoxides in increasing optical purity (93MI2). The trans diols can be easily converted to trans epoxides (90T10515) without the loss of optical purity. Thus, stereochemical transformation of cyclic sulfates and epoxides are gaining increasing importance.

TABLE VI
COMPARISON OF CYCLIC SULFATES AND EPOXIDES

| | Cyclic sulfates | Epoxides |
|------------------------|--|---|
| Basic structure |  |  |
| Ring strain | Ca. 5–6 kcal · mol ⁻¹ | Ca. 27–28 kcal · mol ⁻¹ |
| Reaction type | S _N 2 | S _N 2 |
| Product type | β-Substituted alcohol | β-Substituted alcohol |
| Leaving group | ROSO ₃ ⁻ , average (pK _a of HOSO ₃ = 1.92) | RO ⁻ , poor |
| Reactivity | Reacts under acidic, basic, and neutral conditions without the help of any catalyst | Much less reactive than cyclic sulfate; Lewis acids catalyze the reaction |
| Regioselectivity | Nu attacks less hindered C—O bond, α-substitution preferred | Nu attacks less hindered C—O bond, abnormal regioselectivity |
| Stereochemistry | Inversion | Inversion |
| Double Nu displacement | Possible | Not possible |

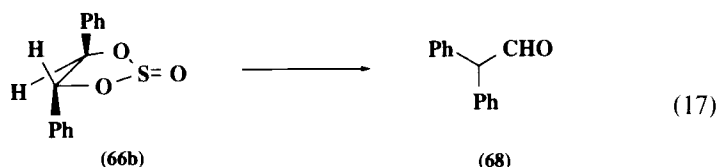
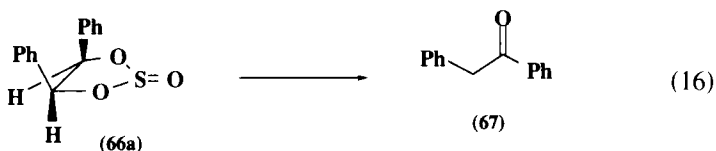
A. THERMAL REARRANGEMENT

Cyclic sulfites undergo facile elimination of sulfur dioxide on heating at high temperature. For example, 4,5-dimethyl-1,3,2-dioxathiolane 2-oxide when heated on calcium oxide at 275°C furnished 2,3-dimethyloxirane and 2-butanone. In contrast, a low yield of butadiene was obtained with passage over clay at 575°C (66HC1). In the case of tetraphenyl-1,3,2-dioxathiolane 2-oxide, a quantitative yield of tetraphenyloxirane was obtained with heating at 145°C [72JOC2589; 82JCR(S)175] (Scheme 13).



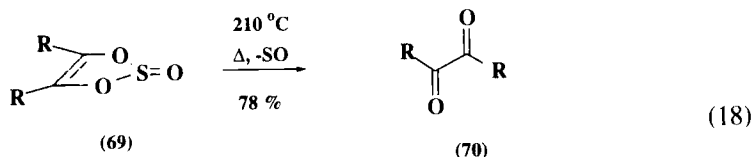
SCHEME 13

Interestingly, thermal decomposition of 4,5-diphenyl-1,3,2-dioxathiolane 2-oxide depends on the stereochemistry of the starting diols. For example, the cyclic sulfite derived from *meso*-hydrobenzoin (**66a**) decomposed on heating to give a good yield of desoxybenzoin (**67**), while the *trans* isomer **66b** (derived from *dl*-hydrobenzoin) furnished diphenylacetaldehyde (**68**) quantitatively [Eqs. (16) and (17)].



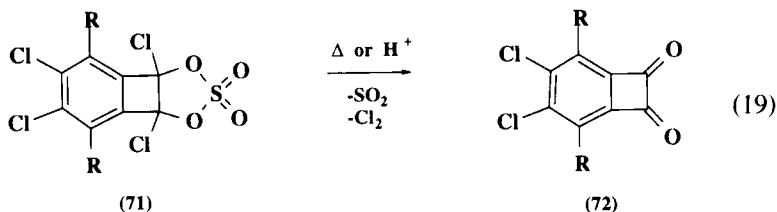
The formation of these products has been rationalized in terms of the pathway shown in Scheme 14, which involves a hydride shift.

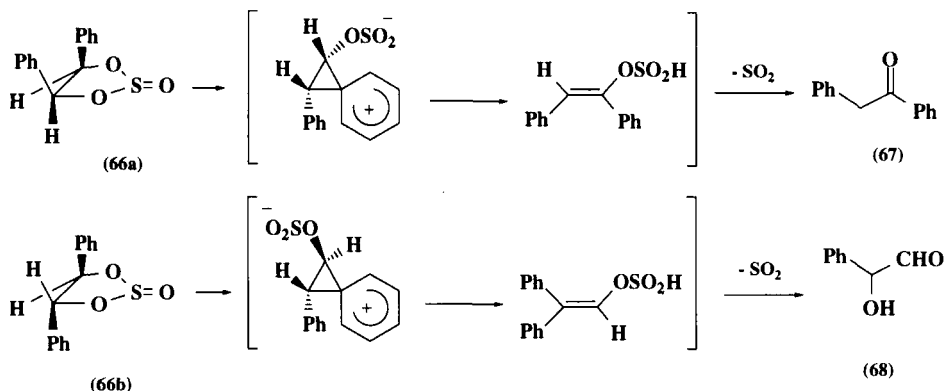
Cyclic sulfites derived from catechol or substituted catechol and ethene-1,2-diol **69** undergo elimination of sulfur monoxide to furnish diketone **70**. For example, 4,5-diphenyl-1,3,2-dioxathiole 2-oxide or 2,2-dioxide furnished benzil [53LA(584)199; 63JOC1075; 86JOC1100] [Eq. (18)].



R = 2,4,6-trimethylphenyl; phenyl; 2,3,4,5,6-pentachlorophenyl;
R-R = *cis,cis*-CH₂-CH=CH-CH=CH-CH₂-

In contrast, the tricyclic sulfate **71** decomposed on heating to 180–200°C or in the presence of dilute HCl to give benzocyclobutane dione **72** (82LA1982) [Eq. (19)].





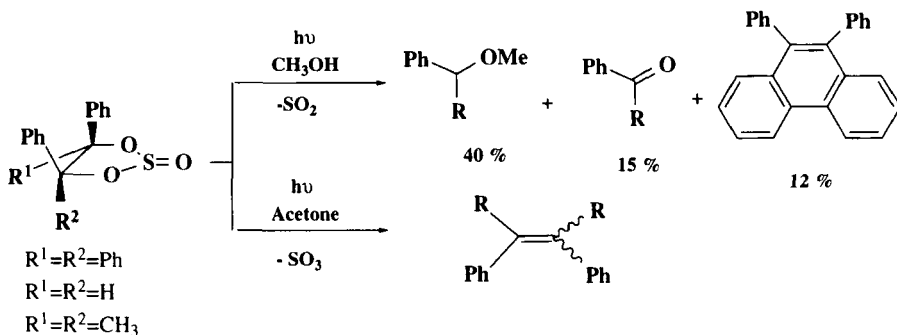
SCHEME 14

B. PHOTOCHEMICAL REARRANGEMENT

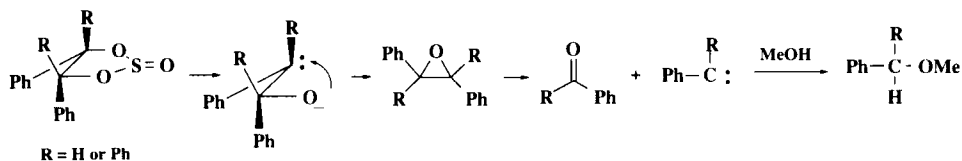
Aryl-substituted cyclic sulfites undergo an interesting photoelimination reaction [72JOC2589; 82JCR(S)175; 84MI1]. For example, 4,4,5,5-tetraphenyl-1,3,2-dioxathiolane 2-oxide, when photolyzed in methanol, furnished a mixture of benzophenone, 9,10-diphenylphenanthrene, and benzhydryl methyl ether. In contrast, photolysis in acetone gave only olefin along with phenanthrene (Scheme 15).

Photolysis of *meso*- and *dl*-4,5-diphenyl-1,3,2-dioxathiolane 2-oxide also furnished similar products. The formation of different products is rationalized in term of the pathways shown in Scheme 16.

The cyclic sulfite loses SO_2 when irradiated in methanol to generate a carbene, which may fragment to diphenylcarbene and benzophenone.

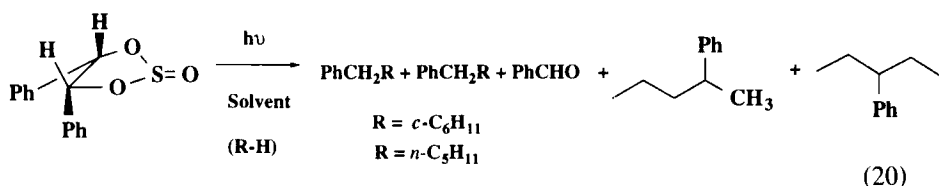


SCHEME 15

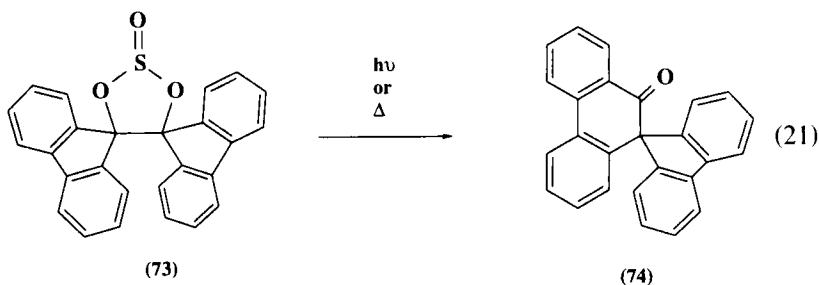


SCHEME 16

Diphenylcarbene undergoes solvolysis to give benzhydryl methyl ether. To substantiate this, photolysis was conducted using cyclohexane and *n*-pentane. In both cases, solvent insertion products were isolated [Eq. (20)].



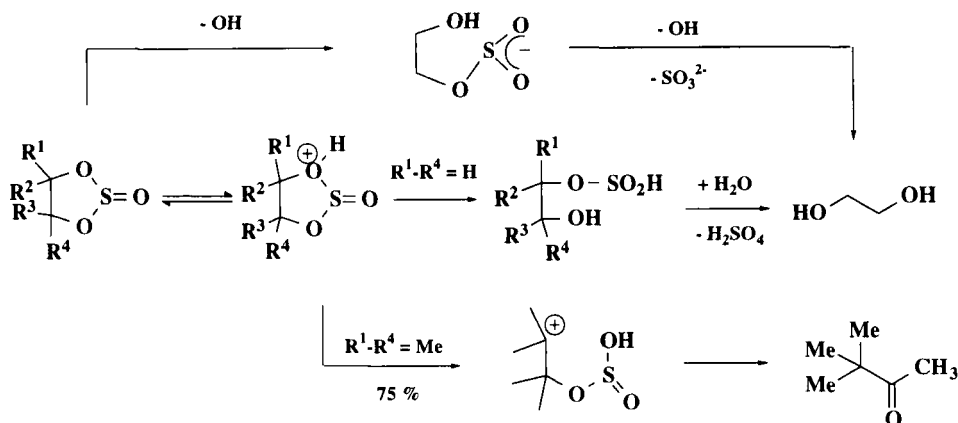
Similarly, fluorenopinacol sulfite **73** undergoes photo- and thermal elimination of SO_2 to generate a carbene, which undergoes subsequent rearrangement to give diphenylenephenanthrene **74** [Eq. (21)].



C. REACTION WITH ELECTROPHILES

1. Reaction with Acids

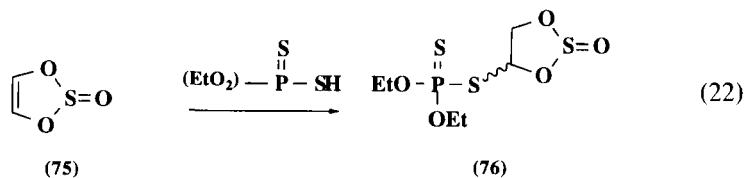
Cyclic sulfites and cyclic sulfates of ethanediol undergo hydrolysis with acids to furnish glycol. The substituted cyclic sulfate, such as tetramethyl-1,3,2-dioxathiolane 2-dioxide, may undergo a pinacol type of rearrangement under acidic conditions to furnish pinacolone in good yield (74JOC3415). The mechanistic pathway is rationalized in Scheme 17.



A detailed study related to acid- or base-catalyzed hydrolysis of various cyclic sulfites and cyclic sulfates has been summarized (66HC1; 84CHEC851; 92S1035).

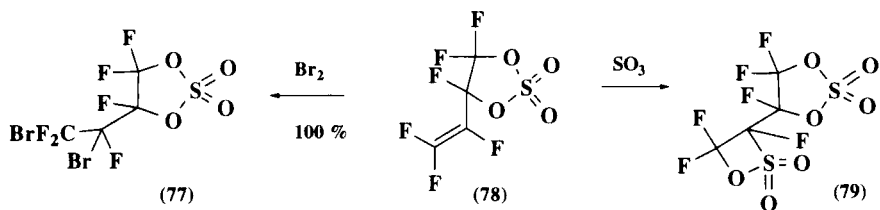
2. Electrophilic Addition to a Double Bond

Cyclic sulfites or cyclic sulfates having a C=C bond either in the ring or on the side chain undergo smooth addition of electrophiles to furnish a good yield of the product. For example, enediol cyclic sulfite **75** undergoes addition of *O,O*-diethyl dithiophosphate to furnish a high yield of addition product **76** (84CHEC851) [Eq. (22)].



In contrast, a cyclic sulfate containing a C=C bond outside the ring, such as in **78**, undergoes either 1,2-addition to afford **77** or cycloaddition to give **79** (Scheme 18).

An interesting cycloaddition of diazomethane on sulfinyldioxycyclobutene (1:1 mixture of syn and anti **80a**:**80b**) has been reported. The anti adduct consisted of a 1:1 mixture of two diastereoisomers (**82a** and **82b**), whereas the syn compound furnished a mixture of diastereoisomers (**81a**



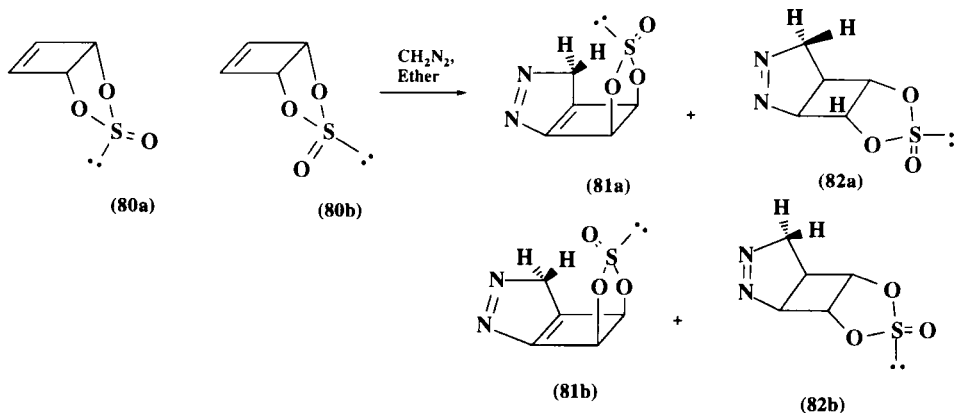
SCHEME 18

and **81b**) in 60:40 ratio, which were separated in pure form (90JOC3311) (Scheme 19).

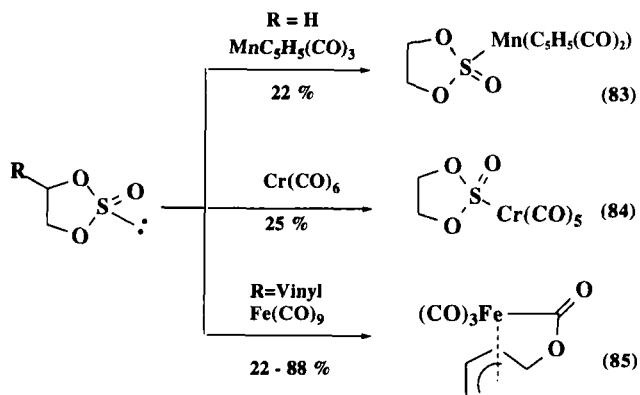
D. REACTION WITH METALS

Ethylene sulfite reacts with metal carbonyls such as manganese and chromium to form a complex in which the sulfur atom functions as an electron donor and is directly attached to the metal center (**83** and **84**) (65CB2248). In contrast, 4-vinyl cyclic sulfite reacts with iron nonacarbonyl to form a π -allyliron complex **85**, with the extrusion of SO_2 (90SL224, 90SL331). Some of these reactions are summarized in Scheme 20.

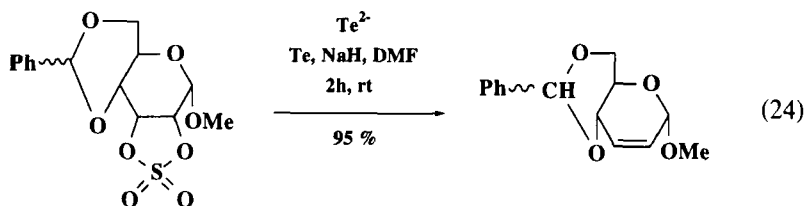
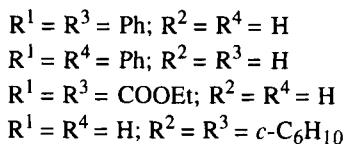
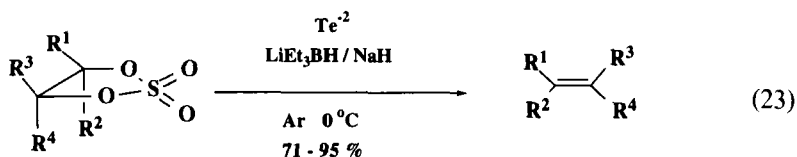
Interestingly, several cyclic sulfates react with telluride ion generated *in situ* by reduction of elemental tellurium to yield alkene under mild conditions (0°C) [Eq. (23)]. For example, 4,5-diphenyl-1,3,2-dioxathiolane 2,2-dioxide gave *trans*-stilbene. Similarly, sugar derivatives can be converted into an unsaturated sugar (95TL7209) [Eq. (24)].



SCHEME 19

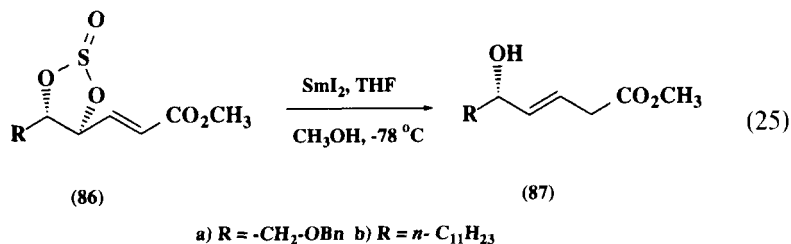


SCHEME 20



E. REARRANGEMENT OF CYCLIC SULFITES AND CYCLIC SULFATES ASSISTED BY LEWIS ACIDS

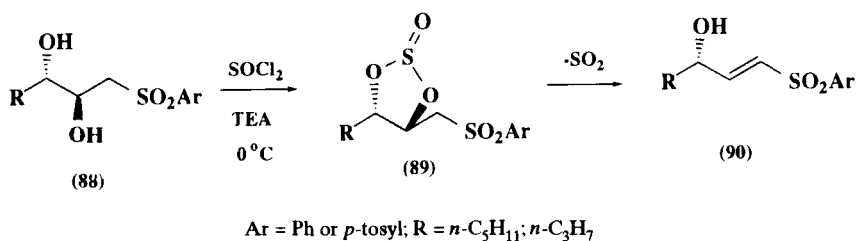
Vinyl-substituted cyclic sulfites undergo rearrangement when treated with SmI_2 (THF) with the loss of SO_2 . For example, cyclic sulfite **86** derived from γ, δ -dihydroxy-(*E*)- α, β -unsaturated ester undergoes facile reductive cleavage with SmI_2 to furnish δ -hydroxy- β, γ -(*E*)-unsaturated ester **87** [Eq. (25)] [93JCS(P1)9].



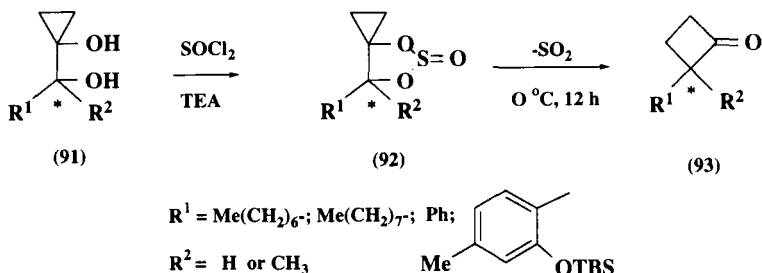
Similarly, β,γ -dihydroxy sulfones **88** when treated with SOCl₂ at 0°C in the presence of triethylamine generated cyclic sulfite **89** *in situ*, which decomposed at room temperature during silica gel chromatography to give γ -hydroxy- α,β -unsaturated sulfone **90** [92JCS(P)405] (Scheme 21).

A similar elimination rearrangement observed in the case of certain cyclic sulfites leads to the enantiospecific synthesis of cyclobutanone. For example, diol **91** when treated with thionyl chloride in the presence of a triethylamine furnished cyclic sulfite **92**, which rearranged to give cyclobutanone **93** (95T5511, 95TL1055) (Scheme 22).

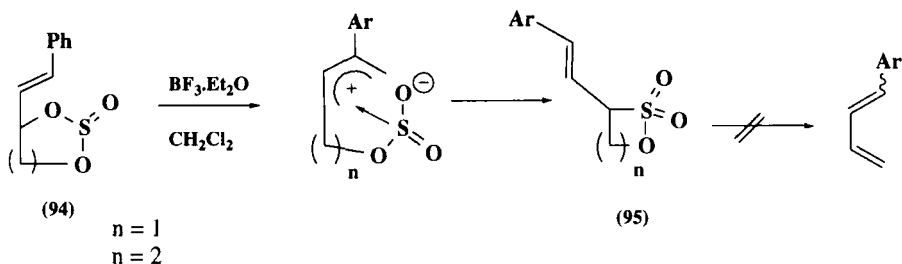
Similarly, vinyl-substituted cyclic sulfites undergo rearrangement in the presence of Lewis acids such as BF₃:Et₂O leading to ring contraction.



SCHEME 21



SCHEME 22

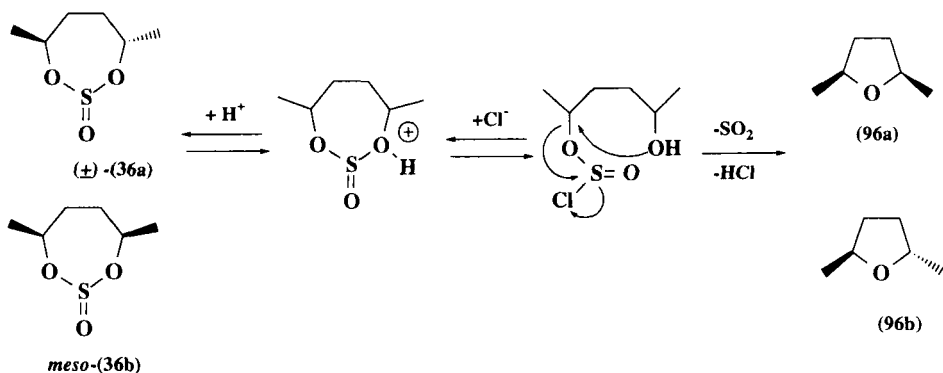


SCHEME 23

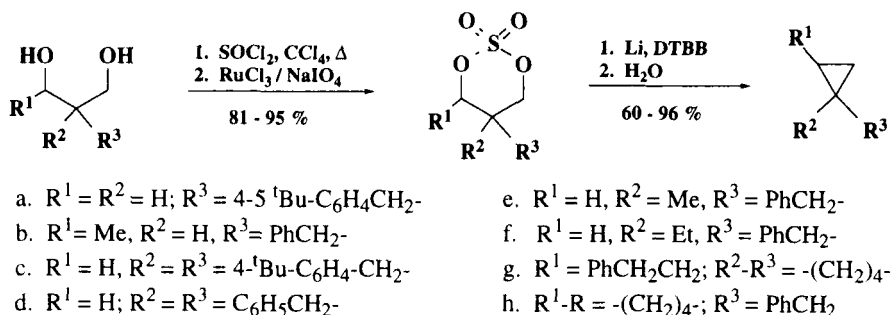
For example, six-membered allylic cyclic sulfites **94** underwent rearrangement to allylic sulfones **95** ($n = 2$) in the presence of a catalytic amount of boron trifluoride etherate in CH_2Cl_2 at room temperature (93TL3667) (Scheme 23).

A similar rearrangement attempted on a five-membered cyclic sulfite failed to yield either a four-membered sulfone or an elimination product. However, tetramethyl-1,3,2-dioxathiolane 2,2-dioxide furnished pinacolone in good yield when heated under aqueous acidic conditions (74JOC3415). In contrast, six-membered cyclic sulfates derived from a number of 1,3-diols underwent a smooth ring contraction reaction when treated with lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 5 mol%) in THF at 0°C followed by hydrolysis as shown in Scheme 24 (95T11445).

A few seven-membered cyclic sulfites derived from *dl*- and *meso*-2,5-hexanediols rearranged to *cis*- and *trans*-2,5-dimethyltetrahydrofuran (**96a** and **96b**) when allowed to stay at room temperature. The *meso* cyclic sulfite



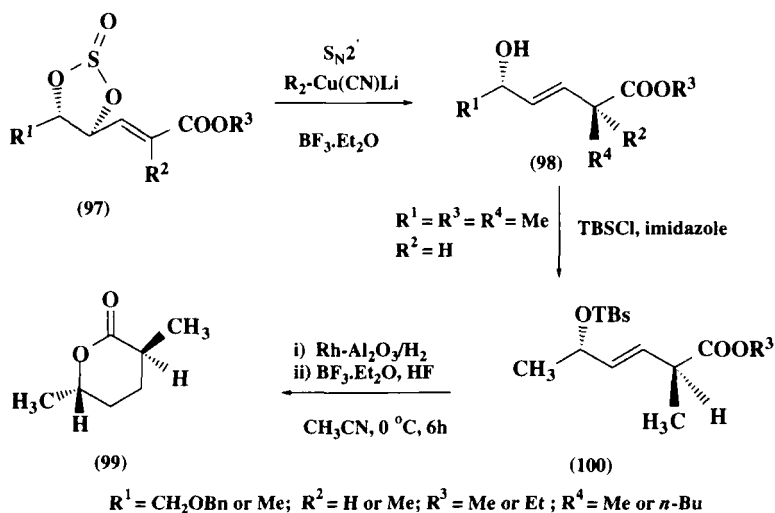
SCHEME 24



SCHEME 25

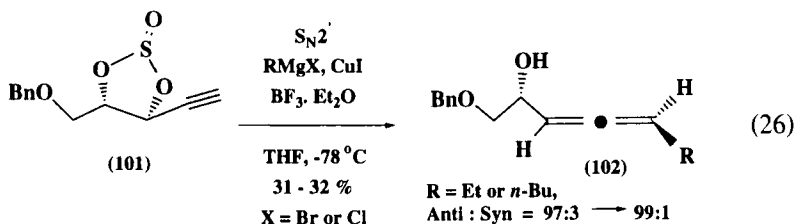
36b rearranged to the trans compound relatively faster than the dl isomer. The mechanism of rearrangement is shown in Scheme 25 (94TA657).

Reaction of cyclic sulfites of γ,δ -dihydroxy-(*E*)- α,β -enoates with $\text{R}_2\text{Cu}(\text{CN})\text{Li} \cdot \text{BF}_3$ or $[\text{RCu}(\text{CN})\text{Li}]\text{BF}_3$ ($\text{R} = \text{CH}_3$, *n*-Bu) afforded the diastereoselective $\text{S}_{\text{N}}2'$ products. Addition of $\text{R}_2\text{Cu}(\text{CN})\text{Li} \cdot \text{BF}_3$ to cyclic sulfite **97** is highly regio-, (*E*)-stereo-, and diastereoselective, affording α -alkylation product **98**. Using this method (2*S*, 5*S*)-*trans*-2-methyl-5-hexanolide (**99**), a pheromone of the carpenter bee *Xylocopa hirsutissima*, has been synthesized (92TA705) (Scheme 26).



SCHEME 26

An analogous strategy has been used to prepare α -allenic alcohols **102** of high enantiopurity by reacting acyclic sulfite **101** of cyclic alkynyl diols with organocopper reagents in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [Eq. (26)] (92TA1509).



F. REACTION WITH NUCLEOPHILES

Nucleophiles can react with cyclic sulfites and cyclic sulfates either at the sulfur atom or at the carbon center of the ring. Cyclic sulfites and cyclic sulfates are known for their high reactivity toward nucleophiles, and in many cases cyclic sulfates are far superior to their epoxide counterparts.

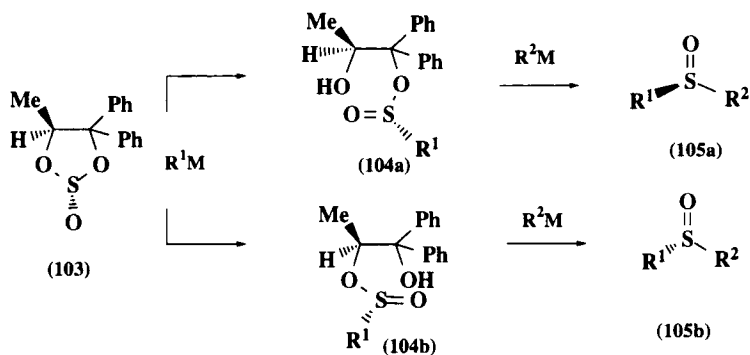
1. Carbon Nucleophiles

One of the earliest nucleophilic reactions of ethylene cyclic sulfite was reported with phenylmagnesium bromide (56JA454). Depending on the reaction conditions, a 3.4 to 23% yield of bromohydrin and a 42–60% yield of diphenyl sulfoxide were isolated [56CI(L)490].

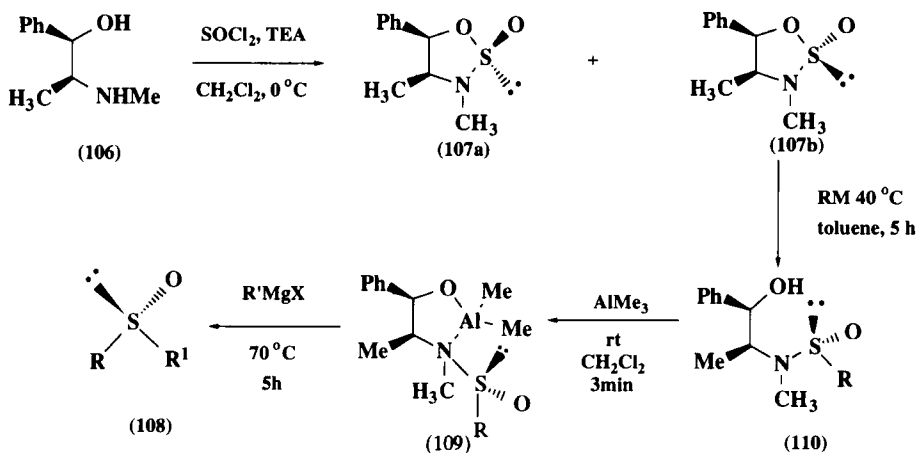
More recently, optically active cyclic sulfite **103** (89TL3659; 91JOC5991) was treated with a variety of organometallic reagents to provide intermediate sulfinate esters **104**. The ratio of ester **104a** to **104b** depends on the nature of the organometallic reagent. Addition of a second organometallic reagent to the purified sulfinate ester furnished an excellent yield of chiral sulfoxide **105** (~100% ee) of predictable absolute configuration. The organometallic reagents were a Grignard reagent or an alkyllithium (93AGE568) (Scheme 27).

Like the reaction of organometallic reagents with cyclic sulfites, reaction of 1,2,3-oxathiazolidine 2-oxide **107** derived from ephedrine (**106**) and thionyl chloride with a Grignard reagent (RMgX) or an alkyllithium ($\text{C}_6\text{H}_5\text{Li}$ or MeLi) furnished a mixture of sulfenamides **110**.

Further reaction of PhLi or PhMgBr with sulfenamide **110** gave only a moderate yield of sulfoxide **108**. However, addition of AlMe_3 to the intermediate sulfenamide **110** followed by addition of Grignard reagent led to the desired sulfoxide **108** in excellent yield and enantiomeric purity (>99% ee) (91TL5885) (Scheme 28).

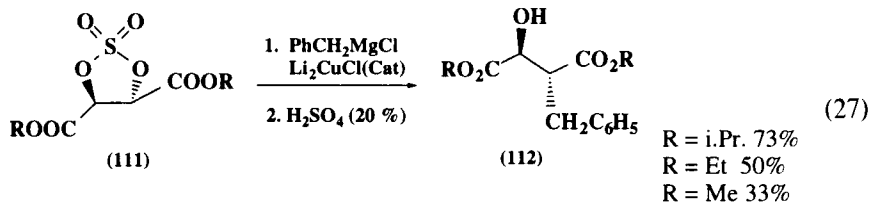


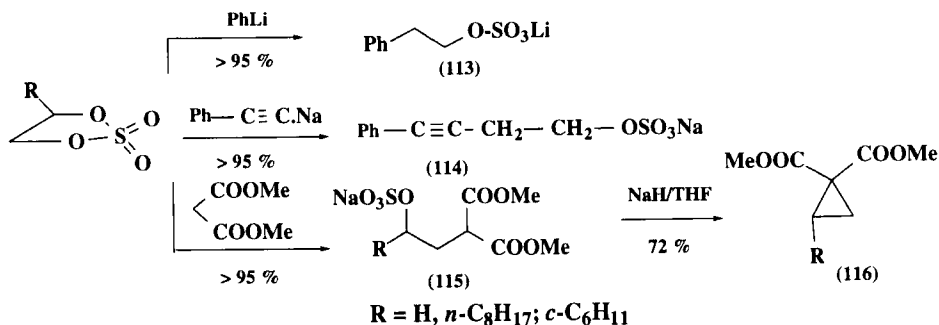
SCHEME 27



SCHEME 28

In contrast to the reaction of cyclic sulfites, the reaction of cyclic sulfates with Grignard reagents or with another organometallic reagent proceeds smoothly, giving rise to substituted ethylene sulfates. Thus, the reaction of benzylmagnesium chloride with cyclic sulfate **111** derived from diisopropyl tartrate gave a 73% yield of *erythro*- β -3-benzylmalate **112** after hydrolysis of the intermediate sulfate (88JA7538) [Eq. (27)].





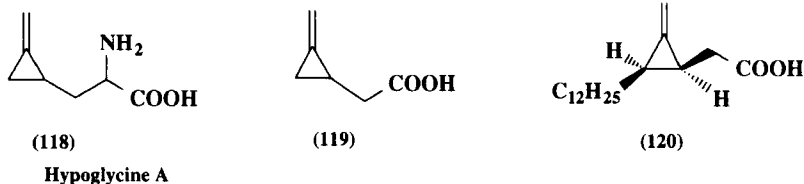
SCHEME 29

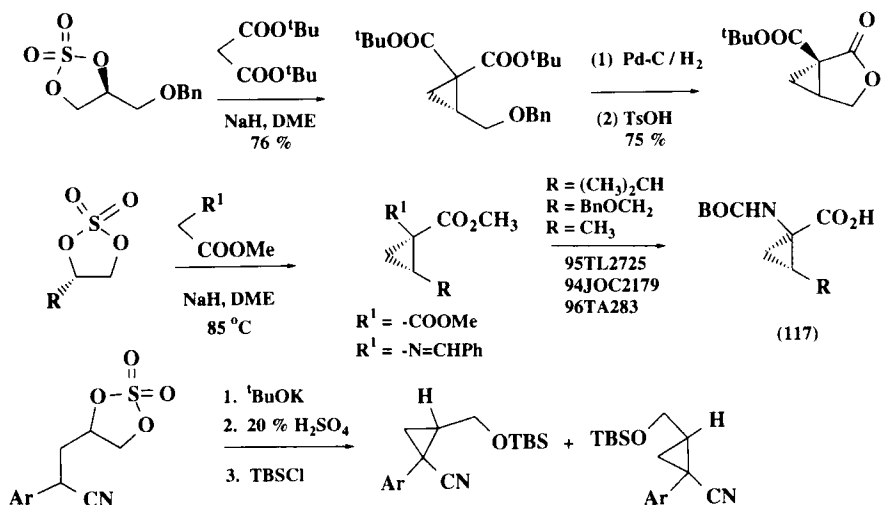
Similar alkyl-substituted malates have been isolated from the reaction of benzylmagnesium chloride and cyclic sulfates derived from dimethyl and diethyl tartrate, though not in good yields (50% and 30%, respectively) [Eq. (27)].

Similarly, other nucleophiles such as phenyllithium and sodium phenylacetylide can react with ethylene sulfate in >95% yield by ring opening of the cyclic sulfate, resulting in β -substituted ethylene sulfate **113** and **114**, as shown in Scheme 29. In the case of sodium dimethyl malonate, the resultant β -substituted sulfate **115** can further undergo a substitution reaction to give cyclopropane derivative **116** because the sulfate moiety is still a leaving group (72JHC891; 88JA7538).

This cyclopropanation reaction has been extensively utilized by Burgess *et al.* (93JOC3767; 94JOC2179; 95TL2725) in the synthesis of optically pure cyclopropane amino acid **117** as shown in Scheme 30. Hercouet *et al.* (96TA283) followed a similar strategy to make cyclopropane amino acid using double nucleophilic displacement of cyclic sulfate with anion generated from methyl benzylidene glycinate and sodium hydride instead of dimethyl malonate in very high yield.

Other cyclopropane derivatives in optically active form have also been prepared via a double displacement reaction of cyclic sulfate, leading to the chiral synthesis of the subunit of CC-1065 (92SL723) (Scheme 30). This cyclopropanation approach has also been utilized in the synthesis of (*R*)-2-methylene cyclopropane acetic acid **119** resulting from the metabolic degradation of hypoglycine **A** **118**.

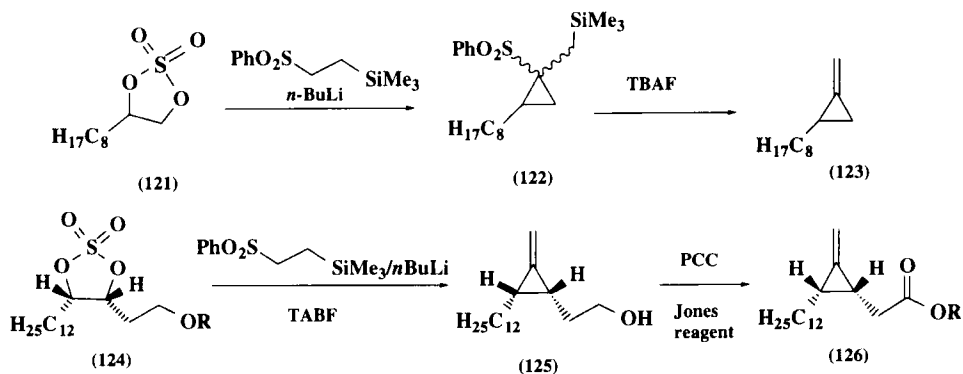




SCHEME 30

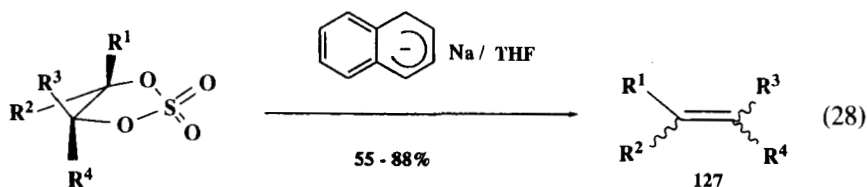
A novel synthetic strategy has been designed using the ring opening of cyclic sulfates **121** and **124** with lithiated β -(trimethylsilyl)ethyl phenyl sulfone followed by elimination of the silyl and sulfone group. An efficient synthesis of methylene cyclopropanes **123** and **126** (92JOC6344), respectively, is produced (Scheme 31).

Similar nucleophilic opening of an epoxide is known to provide a β -hydroxy-substituted ethylene compound that cannot undergo a second nucleophilic substitution reaction, because OH^- is a poor leaving group, unlike $-\text{O}-\text{SO}_3\text{Na}^+$ generated in the reaction of cyclic sulfate.

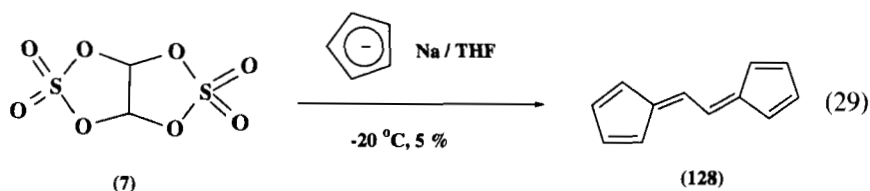


SCHEME 31

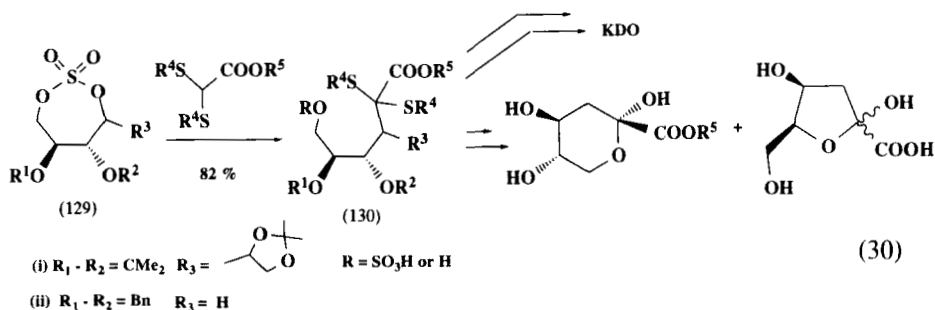
It is in this sense that cyclic sulfates are superior to epoxides. Further examples of double displacement reactions of cyclic sulfates are cited (*vide infra*). In the absence of neighboring group participation, a β -substituted ethylene sulfate may undergo an elimination reaction to furnish olefin. For example, when a cyclic sulfate was treated with sodium naphthalide in THF, only alkene **127** was obtained (90SL479) [Eq. (28)].

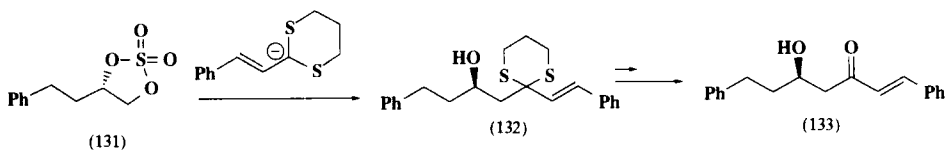


A similar elimination process has been reported in the reaction of sodium cyclopentadienide with glyoxal bis-sulfate **7** to give fulvene derivative **128** (72AGE296) [Eq. (29)].



The reaction of lithium naphthalide with 4-*n*-hexyl-1,3,2-dioxathiolane 2,2-dioxide afforded 1-octene as the sole product (92TL5597). Nucleophilic ring opening of cyclic sulfates by the action of the anion generated from 1,3-dithiane is also reported (74JOC3415). For example, cyclic sulfate **129** derived from a sugar when treated with the sodium salt of dithiane derivatives gave ring-opened product **130**, which was finally converted into *manno*-2-octulosonic acid (KDO) (89TL5477; 90SL311). This strategy has been used to prepare polyhydroxylated pyran and furan from tartaric acid (95BSF829) as shown in Eq. (30).



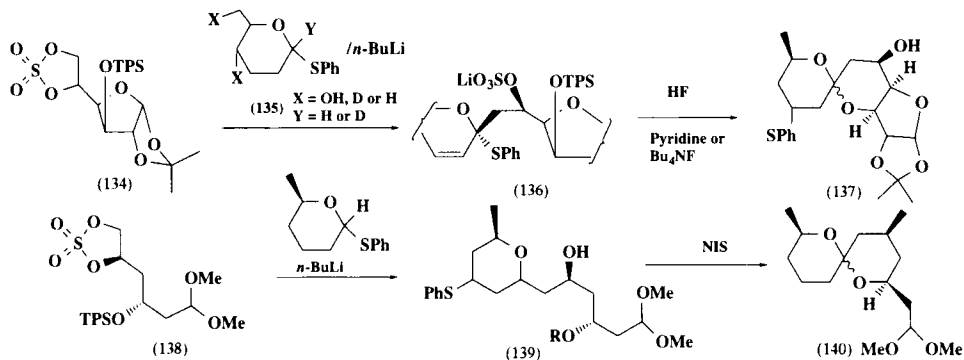


SCHEME 32

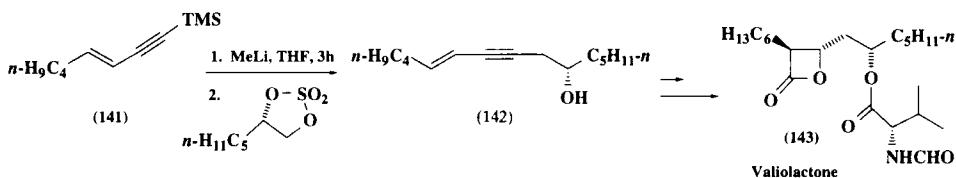
Similarly, Yashabushi ketol **133** was prepared by ring-opening of substituted cyclic sulfate **131** with substituted dithiane (94MI1) (Scheme 32).

Likewise, cyclic sulfate **134** underwent ring opening with the anion derived from α -phenylthio-substituted pyran derivatives **135**, leading to the formation of a spiro ketal **137** (Scheme 33). A similar reaction with cyclic sulfate **138** led to spiro ketal **140**. In contrast, it has been reported that the reaction carried out with the corresponding epoxides did not succeed.

Ley *et al.* (91T9929, 91TL2651) have reported the nucleophilic opening of cyclic sulfates with an anion from **141** (generated from trimethylsilylacetylene and methyl lithium), which furnished intermediate **142** in the synthesis of valiolactone **143** (Scheme 34).

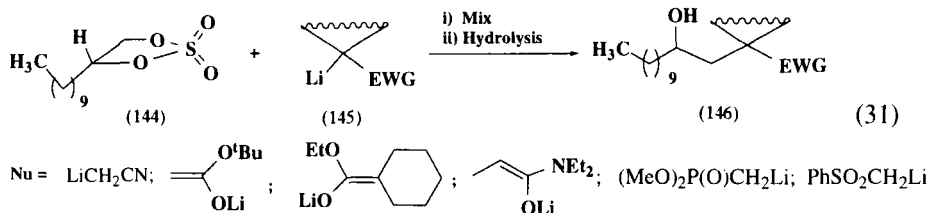


SCHEME 33

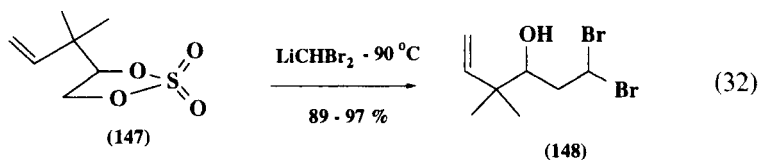


SCHEME 34

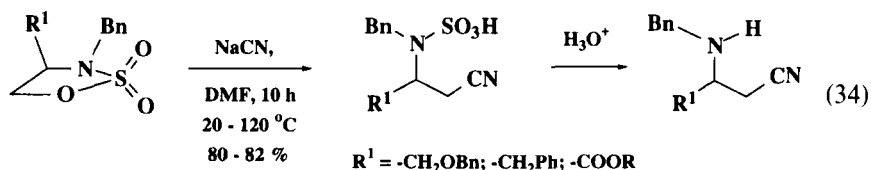
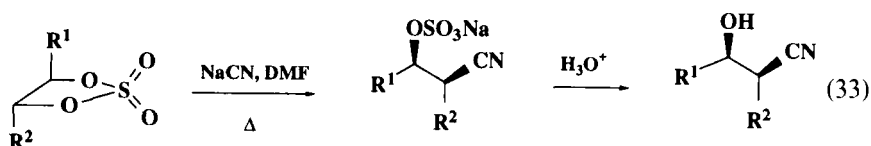
Hoye and Crawford (94JOC520) have reported the reaction of several enolates **145** derived from esters and amides as well as α -sulfonyl-, α -cyano-, and α -phosphonyl-substituted anions with cyclic sulfate **144** to give hydroxylated product **146**. The nucleophilic attack occurred at the terminal carbon [Eq. (31)].



Hoffmann (95TL4595) conducted the nucleophilic opening of cyclic sulfate **147** with lithiated dibromomethane to obtain **148**, which is used as a starting material in the synthesis of Bryostatins [Eq. (32)].



Cyanide has also been used as a nucleophile in the ring opening of several cyclic sulfites (93ACS617; 94ACS183) and sulfates, as well as sulfamides (88JA7538; 90TA881; 91JOC3177; 95TA1667) [Eqs. (33) and (34)]. The nucleophile always attacked the least hindered site and at the activated carbon center.

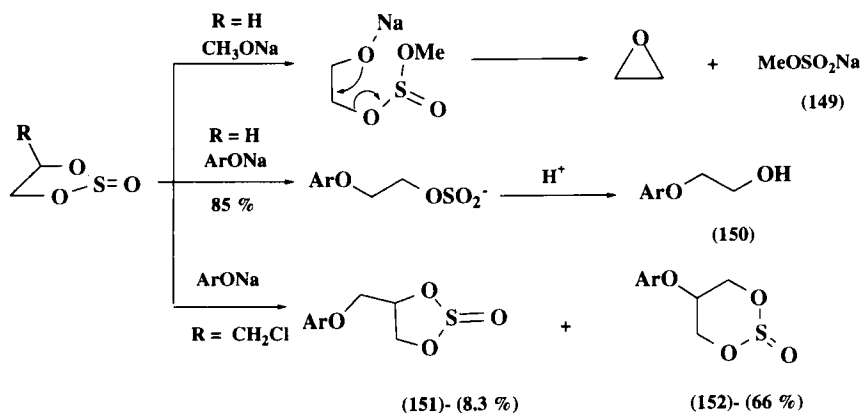


2. Oxygen Nucleophile

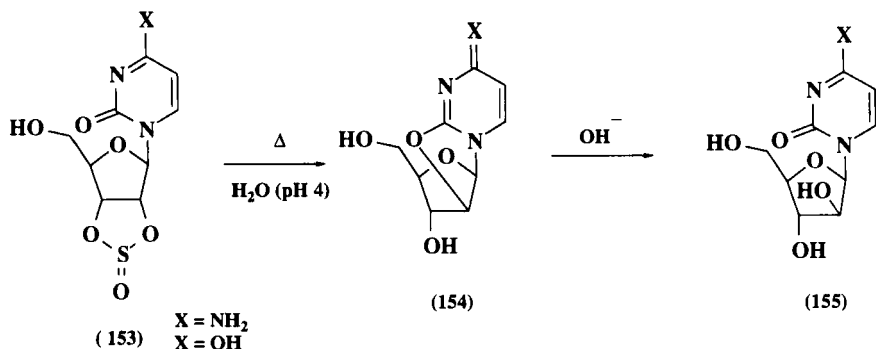
Cyclic sulfites undergo rapid hydrolysis in the presence of aqueous acid. Water acts as a nucleophile to give a tetracoordinated intermediate, which in turn undergoes a fast ring opening to give glycol. In contrast, the rate-determining step in alkali is the attack of OH^- on sulfur, leading to a ring-opened product that subsequently loses HSO_3^- to give ethylene glycol (Scheme 35). Acid- and base-catalyzed hydrolysis of cyclic sulfites has been reviewed by Tillett (76CRV747) (*vide supra*, Section VIII,C,1). Cyclic sulfite treated with sodium methoxide gave ethylene oxide and sodium methyl sulfite **149** as a major product, suggesting that the methoxide ion attacks at the sulfur site only. In contrast, sodium phenolate reacts predominantly at the carbon center to yield an aryl 2-hydroxyethyl ether (**150**) (93ACS617); however, when an appropriate leaving group is present in the side chain of the cyclic sulfite, reaction may also take place at the side chain and rearrangement may also result. For example, 4-chloromethyl-1,3,2-dioxathiolane 2-oxide gave a mixture of products **151** and **152** (Scheme 35) (92S1035).

Because cyclic sulfites are relatively less reactive than cyclic sulfates, *O*-nucleophiles react at the sulfur center, ultimately hydrolyzing them to give the corresponding glycol. However, a very efficient intramolecular ring opening of cyclic sulfite **153** of cytosine or uracil has been reported to give **155**, as shown in Scheme 36 (75BCJ505).

This has led to an inversion at the C_3 center of the sugar backbone. Kiessling *et al.* (94TL7335; 95JOC6254) realized the poor reactivity of cyclic sulfites against oxygen nucleophiles and therefore activated sugar cyclic

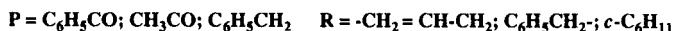
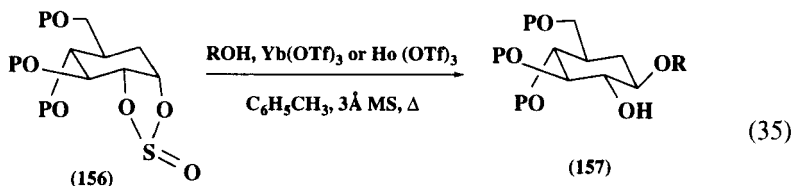


SCHEME 35

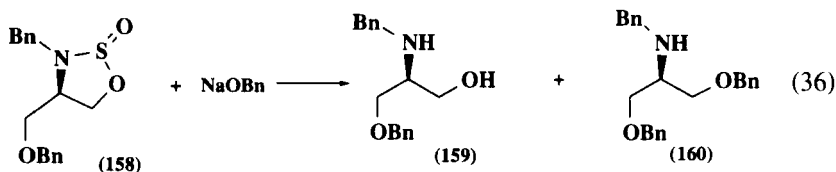


SCHEME 36

sulfites **156** with lanthanide(III) triflates such as $\text{Yb}(\text{OTf})_3$ and $\text{Ho}(\text{OTf})_3$, which then reacted with various alcohols with inversion at the reacting center to furnish selectively β -anomer **157** of the sugar as shown in Eq. (35).

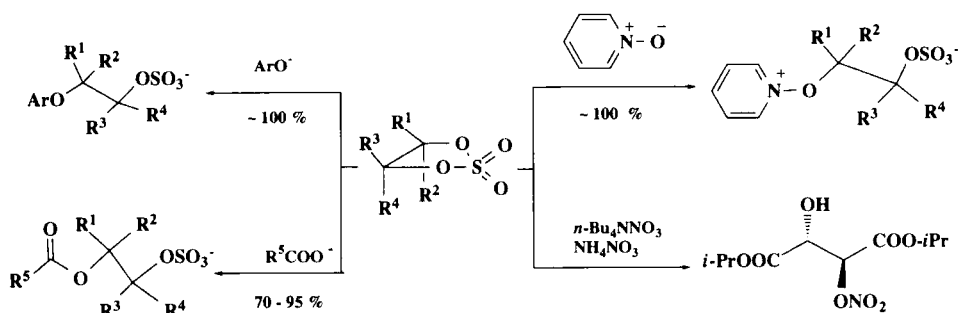


Cyclic sulfamidite **158** also reacts with benzyloxy anions both at the C_5 -carbon center and at the sulfur center, giving rise to a mixture of products [Eq. (36)] (93ACSA617; 95TA1667).



68 : 32

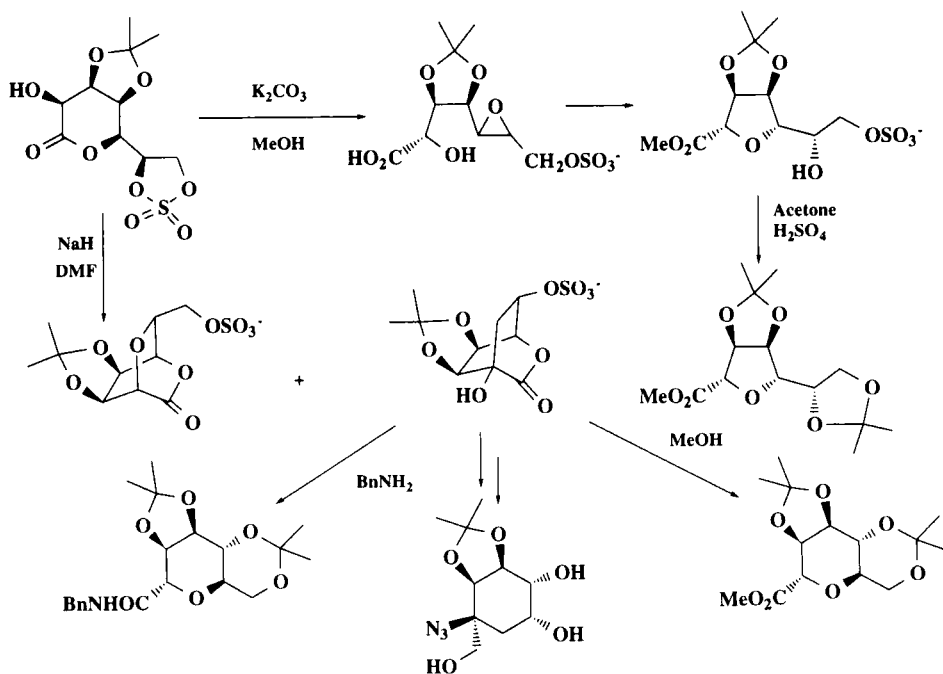
In contrast, cyclic sulfates of 1,2-diols are powerful alkylating agents toward a series of *O*-nucleophiles. Cyclic sulfates react readily at the carbon center with phenolates (72JHC891; 88JA7538; 90JOC1211), amine *N*-oxide (72JHC891), or carboxylate ion (72JHC891; 88JA7538; 89TL655; 90TL3813; 92S989), or even with nitrate (88JA7538) to give ring-opened products as depicted in Scheme 37. In the case of an α -halomethyl-



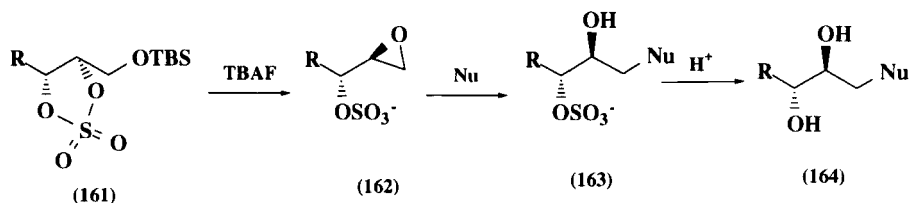
SCHEME 37

substituted cyclic sulfate, reaction of phenolate ion resulted in the formation of an α-aryloxymethyl-substituted epoxide (92EUP515272).

This method has been used for essentially the inversion of the OH group attached to a carbon center especially when carboxylate or nitrate ion nucleophiles are used for the ring opening of a cyclic sulfate. Fleet *et al.* (93TL6115) used an intramolecular OH group as a nucleophile in the ring-opening of a cyclic sulfate, leading to the formation of various glycosides of complex tetrahydrofuran, tetrahydropyran, and cyclohexane derivatives (Scheme 38).



SCHEME 38



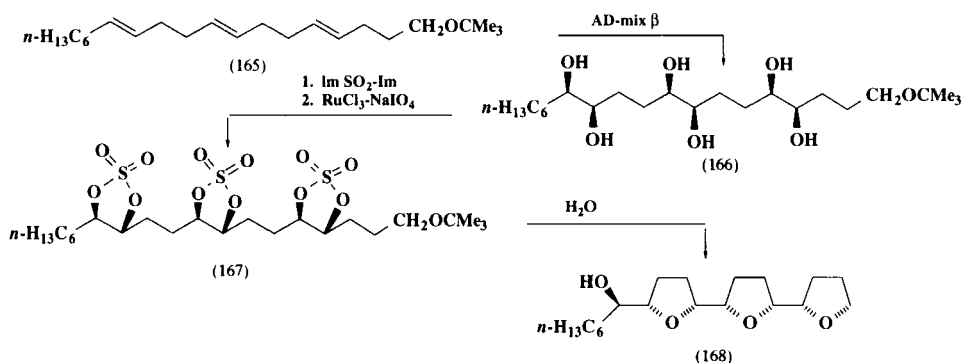
SCHEME 39

Ko has prepared *cis*-epoxides from cyclic sulfates derived from optically active diols prepared by asymmetric dihydroxylation of protected allylic alcohols (94TL3601). For example, cyclic sulfate **161** treated with tetrabutylammonium fluoride gave epoxy sulfate **162** (94JOC2570), which can further react with other nucleophiles to give **164** (Scheme 39). This strategy has been used to synthesize several substituted *erythro*-diols (94JOC2570; 95JOC6250), such as (\pm)-disparlure and gonibutenolides (95TL2101).

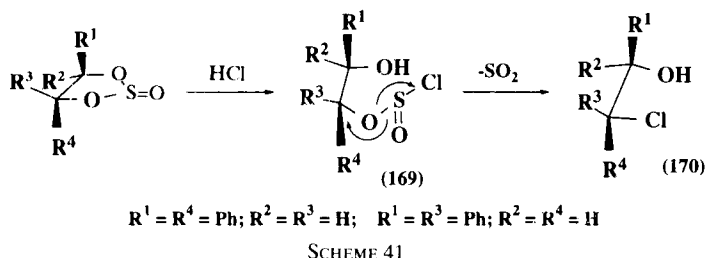
Quite recently, this intramolecular cyclization concept has been utilized for the synthesis of polytetrahydrofurans that occur in macrolides, ionophores, and anti-infective agents. For example, cyclic sulfate **167** heated in aqueous acetonitrile gave polytetrahydrofuran **168** (95CEN41) (Scheme 40). A similar concept of intramolecular cyclization of a hydroxy group generated *in situ* has been used to prepare a trisubstituted tetrahydrofuran (93ACS307).

3. Halide Nucleophiles

Cyclic sulfites obtained from *dl*- and *meso*-hydrobenzoin are known to react with dry HCl gas in dioxane upon heating to furnish *threo*- and *erythro*-



SCHEME 40



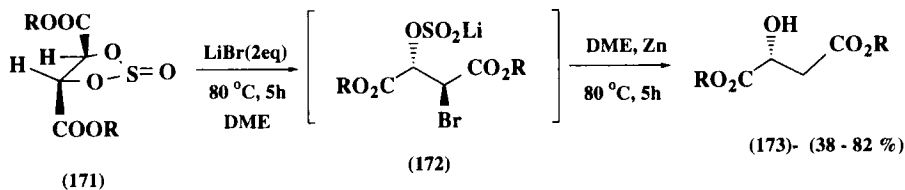
chlorohydrin, respectively (54USP2684977). Since the reaction proceeds without configurational change, the intermediacy of chlorosulfite **169** has been invoked to explain the formation of product **170** (Scheme 41).

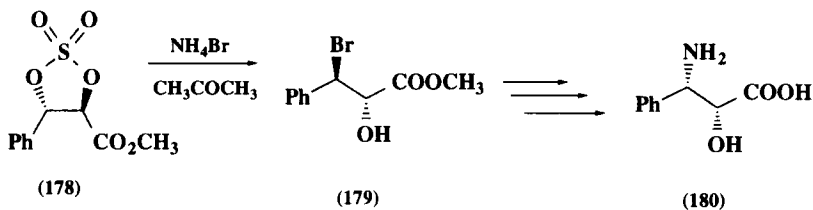
Ethylene sulfite also reacts with chlorine gas under photochemical conditions to form 2-chloroethyl chlorosulfite $\text{ClCH}_2\text{CH}_2\text{OSOCl}$ in excellent yield [67JCS(C)314]. Some anomalous results were reported in the reaction of ethylene sulfite to furnish fluoroethanol, but they could not be substantiated (83MI1). Tewson attempted to carry out nucleophilic opening of a cyclic sulfite derived from a sugar with tetrabutylammonium fluoride, which led to the hydrolysis of cyclic sulfite to furnish the corresponding diol (83JOC3507).

Cyclic sulfites **171** derived from tartaric acid underwent ring opening with LiBr or LiCl in DME or DMF to give dialkyl α -bromo- β -hydroxysuccinate **172**, which was dehalogenated to give optically pure D-malate **173** (91TL3155; 92EUP493187) (Scheme 42).

In contrast to the diminished reactivity of cyclic sulfites toward halide nucleophiles, cyclic sulfates undergo facile ring opening at a carbon center with various halide reagents. Thus, when cyclic sulfates were treated with tetraethyl or tetrabutylammonium fluoride at room temperature in acetone–water, a high yield of fluoro-substituted derivatives **174** was isolated (88JA7538; 89CL1689; 90TL2337) (Scheme 43).

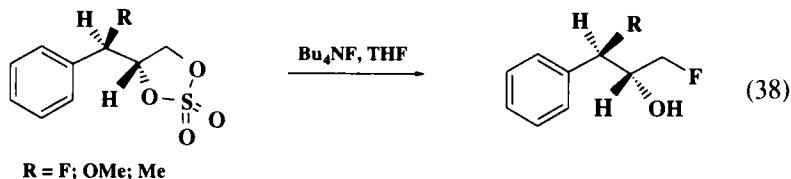
This method has been used to introduce ^{18}F into the carbon skeleton of steroids (90JOC1211). Similarly, several radiolabeled fluorine atoms have





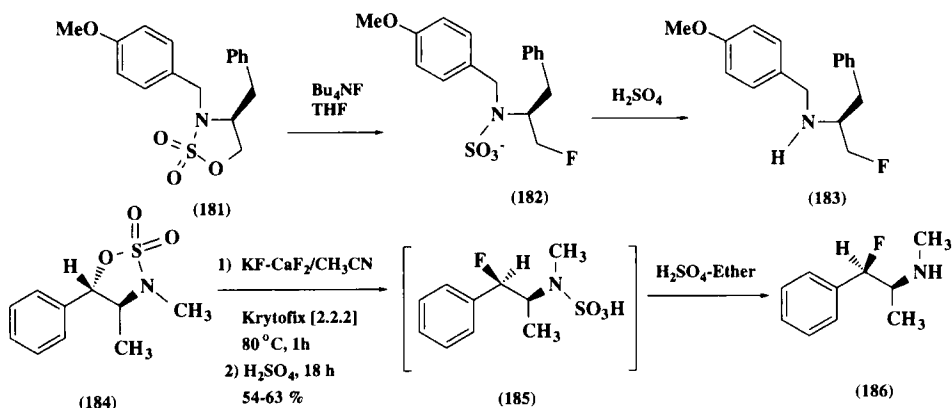
SCHEME 44

[Eq. (38)]. Amino alcohols can be converted into fluoroamines by ring opening of cyclic sulfamidates with KF/CaF_2 or tetrabutylammonium fluoride in THF.



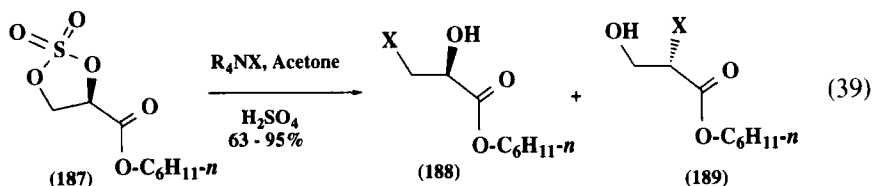
Thus, reaction of cyclic sulfamidate **181** with tetrabutylammonium fluoride in THF, followed by hydrolysis with dilute H_2SO_4 , gave a 61% yield of fluoro compound **183** (91JOC3177).

Similarly, ^{18}F -substituted 1-fluoro-1-deoxyephedrine **186** has been synthesized in 54–63% overall yield from **184** (95JMC810), as described in Scheme 45.

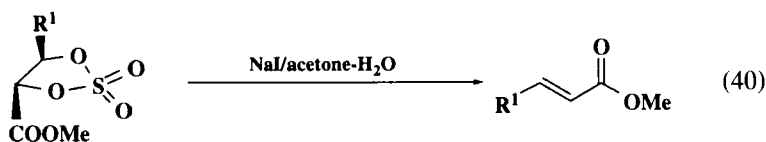


SCHEME 45

Unsymmetrically substituted cyclic sulfates usually give a mixture of regioisomers during nucleophilic ring opening. For example, cyclic sulfate **187** treated with tetrabutylammonium chloride or tetraethylammonium fluoride gave a mixture of α - and β -substituted products **188** and **189** in 6:1 to 5:1 ratios, respectively [Eq. (39)].



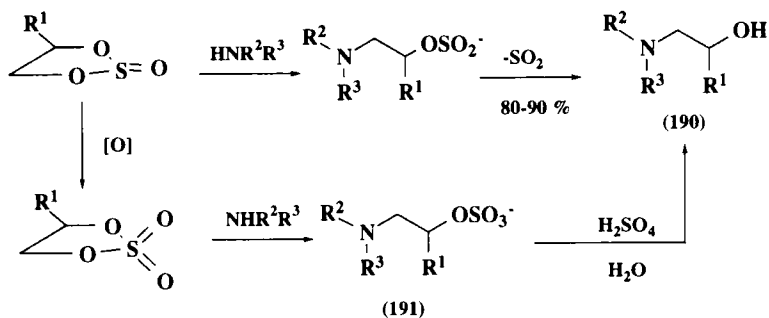
In contrast, when cyclic sulfates were treated with NaI, no iodosubstituted products were isolated; instead, an α,β -unsaturated ester was formed in 85% yield (93UP1) [Eq. (40)].



4. Nitrogen Nucleophiles

The most extensive studies of cyclic sulfites and cyclic sulfates have been done with nitrogen nucleophiles. Several reactions of cyclic sulfites and cyclic sulfates with amines and azides have been summarized in a review (92S1035). Cyclic sulfites react with primary, secondary, and tertiary amines with ring opening followed by loss of SO_2 to give amino alcohols **190**, whereas cyclic sulfates furnish β -amino sulfate salt **191** in good to excellent yields. These need to be further hydrolyzed to give amino alcohols **190**. Earlier, Tomalia and Falk (72JHC891) reported reactions of several aniline derivatives and primary and secondary amines to give a high yield of β -amino sulfates, which may be hydrolyzed to the corresponding amino alcohols (Scheme 46).

Among all the nucleophiles, azide ion has been found to be the most reactive toward nucleophilic ring opening of cyclic sulfites as well as sulfates. Tewson and Welch (83MI1) have reported a stereoselective opening of a cyclic sulfite derived from sugar **192** with sodium or lithium azide in HMPT to give an excellent yield of azido alcohol **193**. In the case of bicyclic sulfite **194** derived from a sugar, terminal attack of azide ion has been found to be favored to give **195** (85TL6343). Guiller *et al.* have also activated an

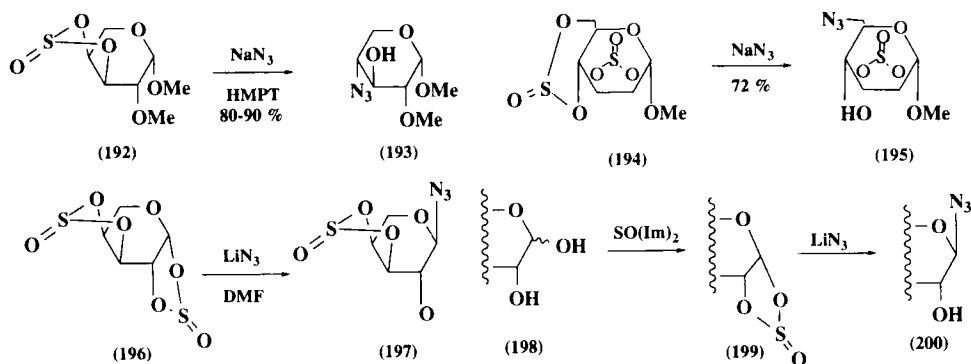


SCHEME 46

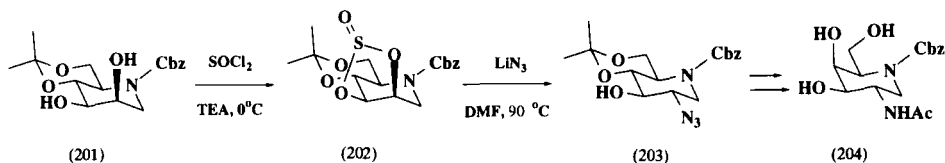
anomeric hydroxyl group as a cyclic sulfite in monosaccharides where other hydroxyl groups are protected. The cyclic sulfite reacted with N_3^- to afford one anomeric derivative **197** solely (86MI1, 86MI2). They have also shown that when two cyclic sulfites are present in monosaccharides, the azide ion reacts preferably at the anomeric center to give 1,2-*trans*-glycoside, and the other cyclic sulfite group functions as a protecting group of other hydroxyl groups (88MI1). This strategy has been used to prepare a number of 1,2-*trans*-glycosyl azides from various sugar cyclic sulfates (94TL3913) (Scheme 47).

Aminonojirimycin has been prepared from 1-deoxynojirimycin via cyclic sulfite. 1-Deoxynojirimycin was converted into protected diol **201**, which was treated with thionyl chloride to form cyclic sulfite **202**.

Treatment of cyclic sulfite with lithium azide in DMF gave azido alcohol **203**, which was converted finally into 2-acetamido-1,2-dideoxy-D-galactanojirimycin **204** (89EUP298350; 90MI1) (Scheme 48). A smooth



SCHEME 47

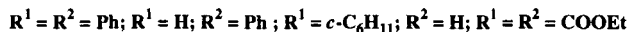
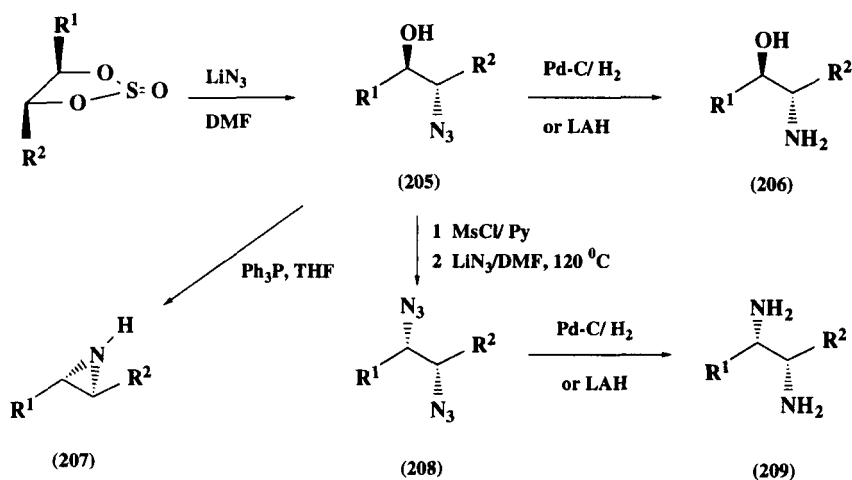


SCHEME 48

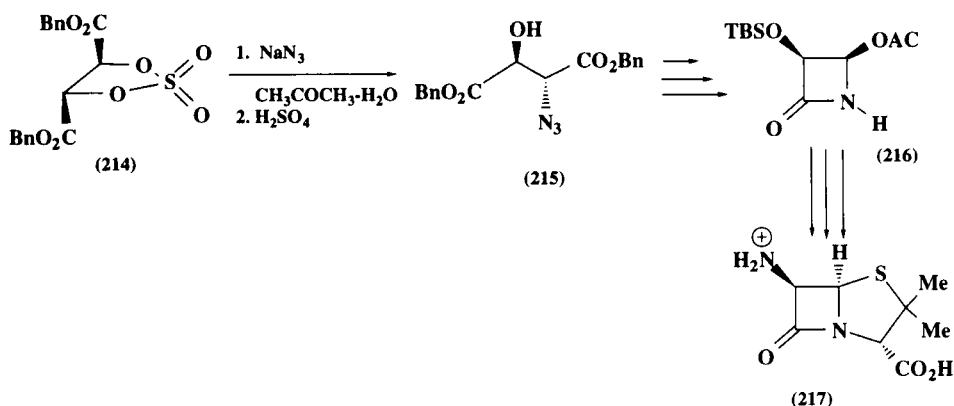
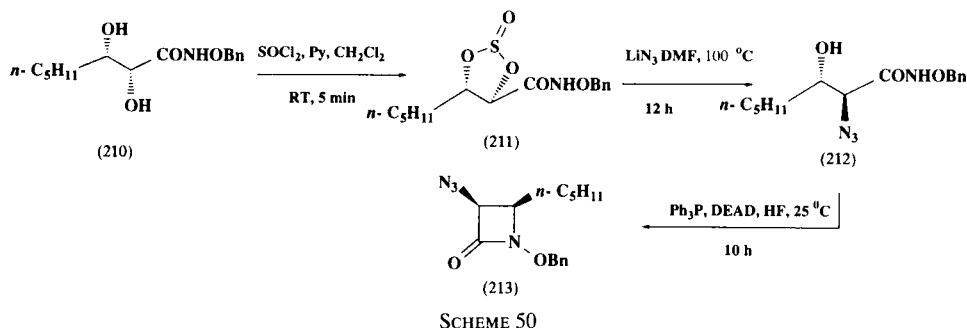
opening of several 1,2-cyclic sulfites with LiN_3 in DMF has been reported to furnish a 76–85% yield of azido alcohols **205**, which were readily converted into amino alcohol **206**, aziridine **207**, and diamines **209** [91-JCS(CC)95; 93ACS617; 94ACS183, 94MI2] (Scheme 49). Azide ion always attacked the cyclic sulfite from the least hindered site.

In the case of an ester cyclic sulfite, reaction was carried out at lower temperature (*ca.* -20°C) to furnish an azido alcohol. Higher reaction temperatures led to elimination, giving rise only to azido maleate (93JA10267).

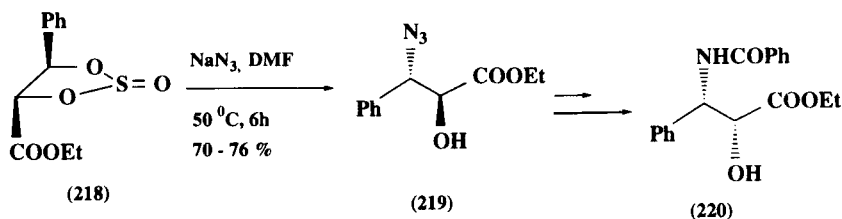
Cyclic sulfite **211** derived from α,β -dihydroxy hydroxamate **210** underwent stereoselective ring opening at the α position to give azido alcohol **212**, which further cyclized to β -lactam derivative **213** under Mitsunobu conditions (90TL4317) (Scheme 50). A similar β -lactam synthesis by the ring opening of cyclic sulfate **214** derived from tartaric acid with azide nucleophile followed by reduction has been reported (90JOC5110) (Scheme 51).

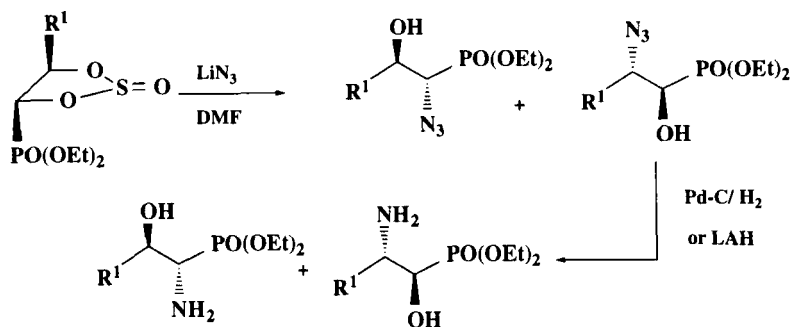


SCHEME 49



A cyclic sulfite has been utilized for the stereoselective synthesis of 3-phenylisoserine, an important side-chain fragment of Taxol [95IJC(B)471]. Cyclic sulfite **218** derived from ethyl (2*S*, 3*R*)-dihydroxy-3-phenylpropionate underwent stereoselective ring opening with NaN₃/DMF/50°C/6 h to give azido alcohol **219** in 70–76% yield, which then was reduced to 3-phenylisoserine ester **220** (Scheme 52).



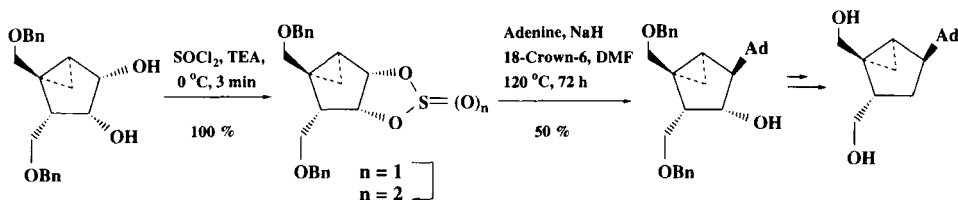
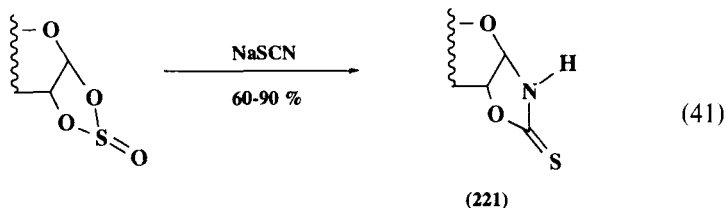


SCHEME 53

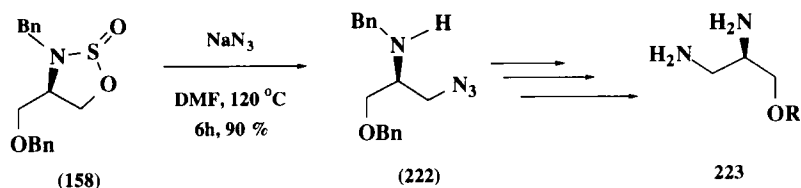
A similar strategy has been used to prepare an aminophosphonic acid via a cyclic sulfite as shown in Scheme 53 [95IJC(B)1023].

Very recently, Jeong and Marquez have utilized the intermediacy of cyclic sulfite to prepare anti-HIV active nucleoside, 9-[2',3'-dideoxy-3'-C-(hydroxymethyl)]- β -*erythro*-pentafuranosyladenine (96TL2353) (Scheme 54). The corresponding cyclic sulfates, although far more reactive than the cyclic sulfites, were found to be unstable.

Some sugar cyclic sulfites are also opened with sodium thiocyanate. Interestingly, they gave exclusively *cis*-fused 1,2-oxazolidine 2-thione, **221** (95TL5347) [Eq. (41)].



SCHEME 54

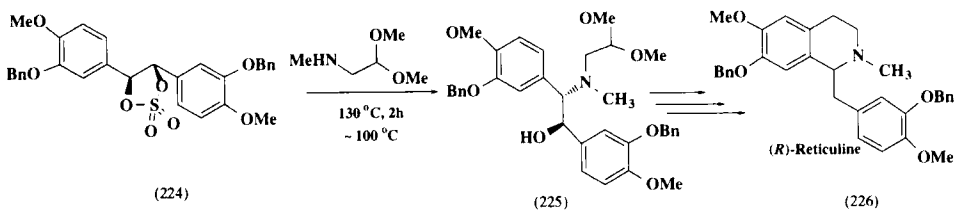


SCHEME 55

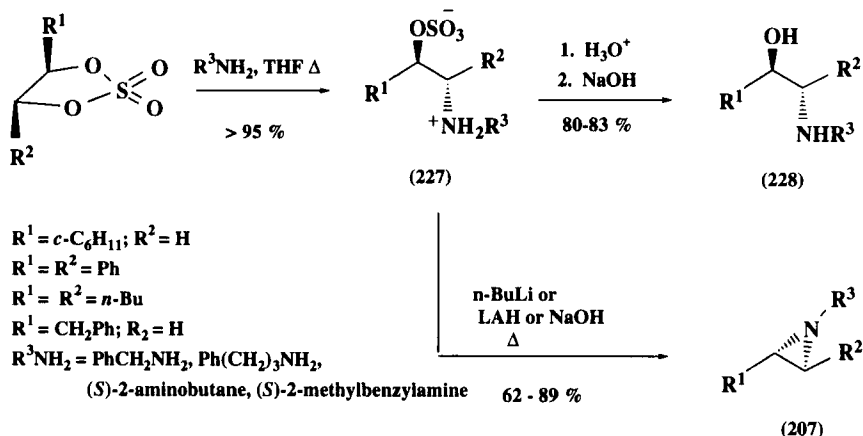
As with a cyclic sulfite, cyclic sulfamidite **158** also undergoes stereoselective ring opening to furnish azido amine **222**, which is a precursor for the synthesis of diamines **223** (95TA1667) (Scheme 55). The azide nucleophile always attacks the carbon having oxygen functionality.

Nucleophilic opening of cyclic sulfates with nitrogen nucleophiles proceeds more smoothly and under much milder conditions than that of cyclic sulfites. Also, in the case of cyclic sulfites having unactivated carbons, nucleophilic opening of the ring may result in a competitive reaction, i.e., the reaction of a nucleophile at a S vs C center (*vide supra*). In such cases, use of a cyclic sulfate is recommended because the cyclic sulfate undergoes nucleophilic opening under much milder conditions. In contrast, some cyclic sulfates have been found to be quite unstable because of large ring strain and undergo instantaneous decomposition. For example, 4-phenyl-5-methoxycarbonyl-1,3,2-dioxathiolane 2,2-dioxide (Scheme 52) [95IJC(B)471], 4-*p*-methoxyphenyl-5-methoxycarbonyl-1,3,2-dioxathiolane 2,2-dioxide (Scheme 72) (95JOC5983), 4-phenyl-5-diethylphosphonyl-1,3,2-dioxathiolane 2,2-dioxide (Scheme 53) [95IJC(B)1023], and cyclophenyl derivative (Scheme 54) (96TL2353) have been found to be quite unstable and sometimes difficult to prepare. In such cases, use of a cyclic sulfite is recommended.

(*R*)-Reticuline **226** was prepared by the nucleophilic opening of diaryl-cyclic sulfate **224** with methylaminoacetaldehyde dimethyl acetal to give intermediate amino alcohol **225**, which was finally transformed to (*R*)-reticuline **226** (Scheme 56) (90TL7591; 91TL1775; 92EUP471303).



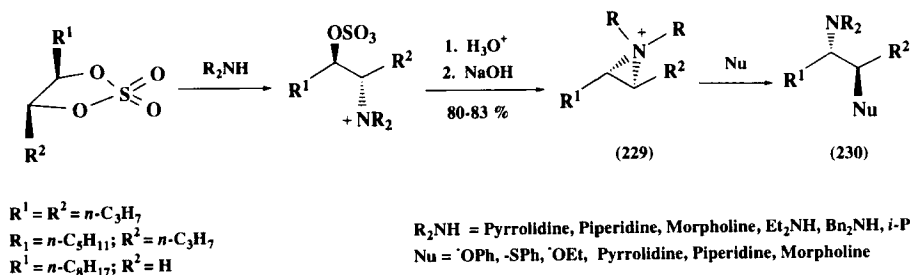
SCHEME 56



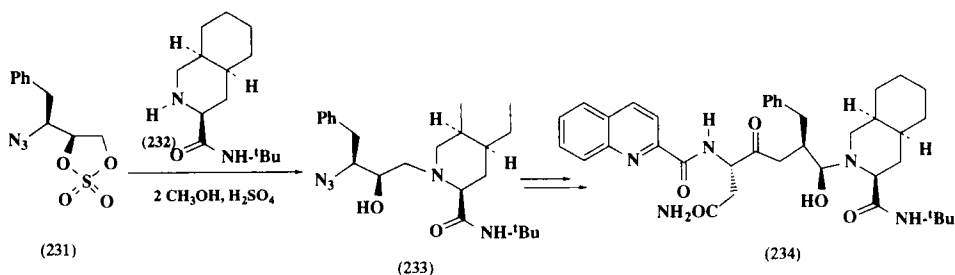
SCHEME 57

Like cyclic sulfites, cyclic sulfates react with tertiary amines or pyridinium derivatives to afford sulfatobetaines (75JPR943). Several cyclic sulfates have been reacted with chiral and achiral primary amines, leading to the formation of β -amino sulfates **227**, which furnish β -amino alcohol **228** upon hydrolysis (89TL2623). Such a nucleophilic displacement has been extensively used in the preparation of drugs and drug intermediates (85MIP2; 86MIP1). However, the sulfate group in the β -amino sulfate is itself a leaving group (79MI1). Thus, in the presence of a suitable base such as n -BuLi or NaOH or LiAlH_4 , the adjacent amino group can displace the β -sulfate moiety to furnish aziridine **207**. Such a double displacement reaction is not available in the case of a reaction of an epoxide with an amine (*vide supra*) (Scheme 57).

If the cyclic sulfate is initially opened with a *sec*-amine, the intramolecular displacement leads to a quaternary aziridine ion **229**, which can be opened by a second nucleophile in a sequential triple displacement (95TL9241) leading to substituted amines **230**, as shown in Scheme 58.



SCHEME 58

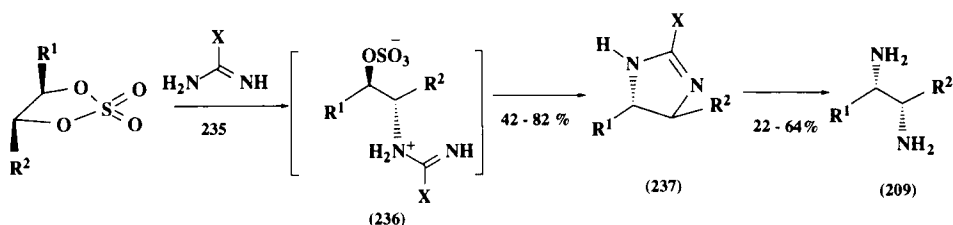


SCHEME 59

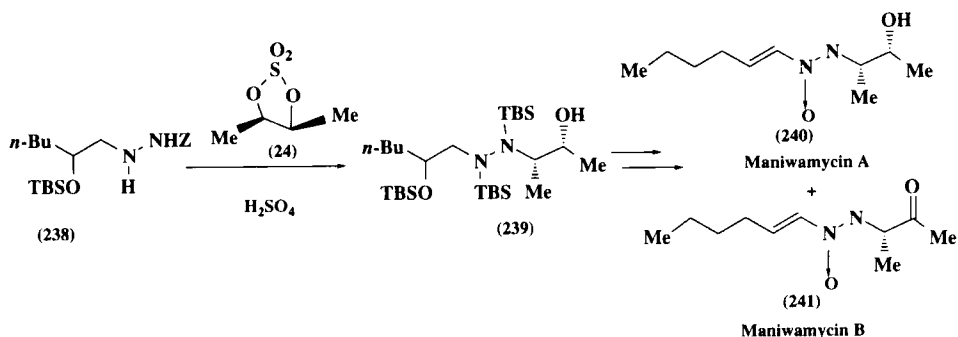
Ring opening of cyclic sulfate **231** with secondary amine **232** has been utilized in the synthesis of HIV-protease inhibitor **234** (94JOC3656) (Scheme 59).

Intramolecular double displacement of cyclic sulfates has been successfully utilized in the synthesis of diamines **209** using benzamidine **235** as a nucleophile (91TL999), though this method did not furnish a satisfactory yield of diamine **209**. The intermediate 4,5-dihydroimidazole **237** was found to be difficult to hydrolyze to diamine **209** in satisfactory yield (Scheme 60).

Substituted hydrazine **238** has been used as a nucleophile for stereoselective ring opening of cyclic sulfate **24** in the synthesis of Maniwamycins A and B (93TL6095), as shown in Scheme 61.

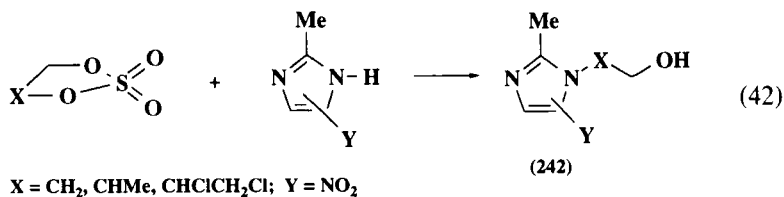


SCHEME 60

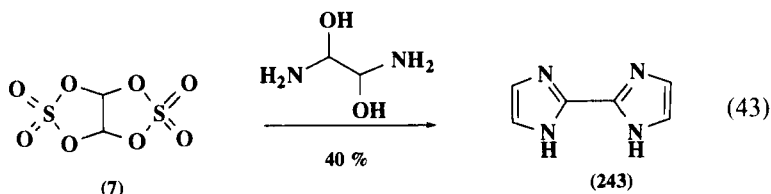


SCHEME 61

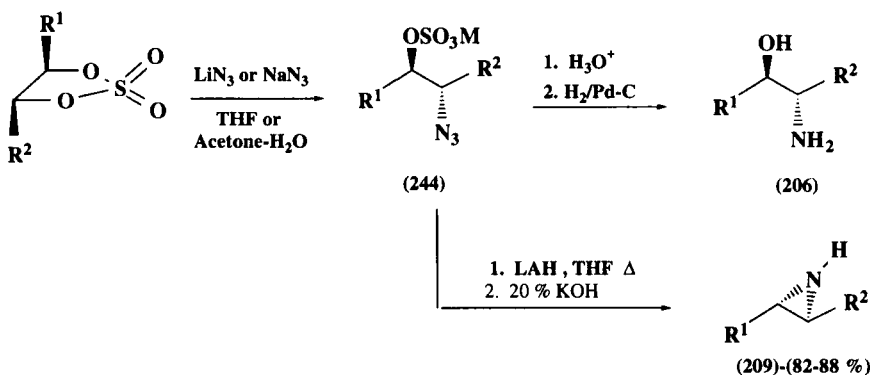
Similarly, imidazole can be used for opening of a cyclic sulfate to provide *N*-(hydroxyalkyl)imidazoles (89EUP324691; 90EUP399901; 92MI2) [Eq. (42)].



A few bis-imidazole derivatives **243** were synthesized using glyoxal sulfate (87KGS1069) [Eq. (43)].



Among all the nucleophiles, azide ion has been found to be the most reactive nucleophile for ring opening of a cyclic sulfate. Various cyclic sulfates that have been reacted with azide ion are listed in Table VII. Opening of a cyclic sulfate with LiN_3 gave azido sulfate **244** (89TL2623), which was subsequently transformed to aziridine **209** by reduction with LAH or hydrolyzed to an azido alcohol and finally reduced to amino alcohol **206** (Scheme 62). Cyclic sulfate containing an acid-labile group can be



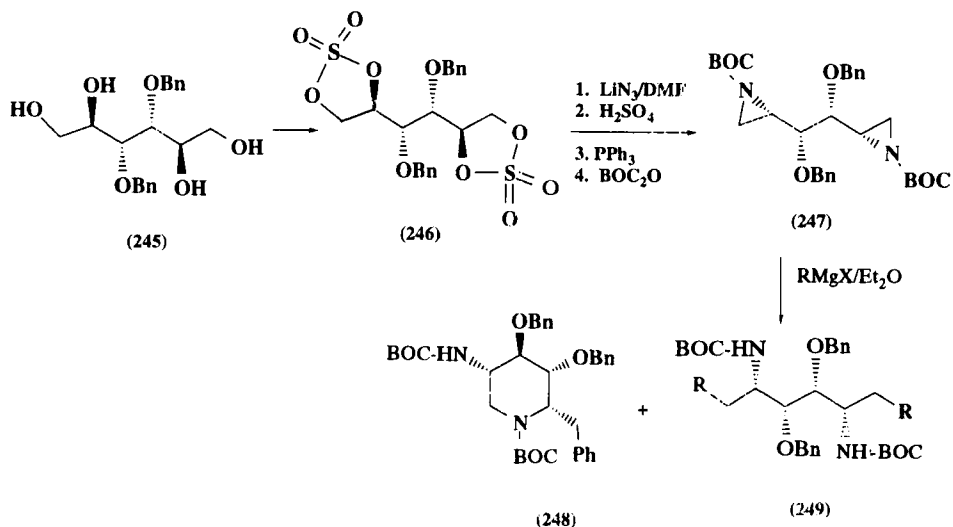
SCHEME 62

TABLE VII

| R ¹ | R ² | Reference |
|---|---|---------------|
| (R)-Cyclohexyl | H | 89TL2623 |
| (R)- <i>n</i> -Bu | <i>n</i> -Bu | 89TL2623 |
| | | 89TL655 |
| COOCH ₃ | | 89TL655 |
| H | Et | 89TL655 |
| CO ₂ - <i>i</i> -Pr | CH ₂ OTBS | 89TL655 |
| CO ₂ Et | CO ₂ - <i>i</i> -Pr | 88JA7538 |
| CO ₂ Me | CO ₂ Et | 88JA7538 |
| CO ₂ Bn | CO ₂ Me | 88JA7538 |
| Bn | CO ₂ Bn | 90JOC5110 |
| (<i>S</i>)-BnO-(CH ₂) ₄ | PO(OMe) ₂ | 94JOC7930 |
| (<i>R</i>)/(<i>S</i>)- <i>n</i> -C ₅ H ₁₁ | (<i>S</i>)-(CH ₂) ₄ OBn | 91JOC1386 |
| (CH ₃) ₂ CH | (<i>R</i>)-(<i>S</i>)- <i>n</i> -C ₅ H ₁₁ | 90TL3637 |
| | COOEt | 94T9181 |
| H | SiMe ₃ | 94JCS(P1)1061 |
| | | 92MI3 |

hydrolyzed using a catalytic amount of sulfuric acid without the loss of a protecting group (73JOC3510; 89TL655).

This method has been used for the synthesis of α -silylaziridine [94-JCS(P1)1061] and HIV-protease inhibitor and deoxyamino azasugar **248** (93H577). Thus, bicyclic sulfate **246** derived from mannitol was opened with lithium azide in DMF to form bisaziridine **247**, which was reacted with suitable Grignard reagent to give HIV protease inhibitor **249** and aminodeoxy-azasugar **248**, as shown in Scheme 63.

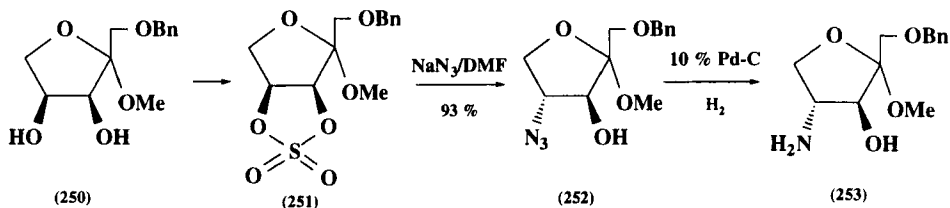


SCHEME 63

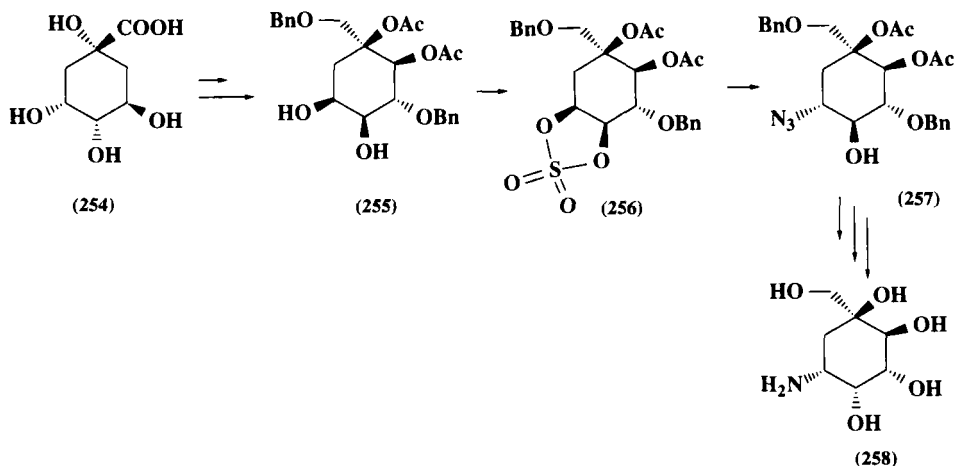
Vanderwalle prepared amino-substituted tetrahydrofuran derivative **253** from L-robulose (90TL2337) (Scheme 64).

Shing and Van recently prepared Valiolamine (**258**) from (–)-quinic acid (**254**) via stereoselective opening of cyclic sulfate **256** as shown in Scheme 65 (95AGE1643). Valiolamine is a glycosidase inhibitor and is used in the management of diabetes. Machinaga and Kibayashi synthesized several chiral pyrrolidines **262** by opening of seven-membered cyclic sulfate **259** with azide to give an azido alcohol, which was then cyclized via **261** to pyrrolidine **262** (90TL3637) (Scheme 66) (91JOC1386).

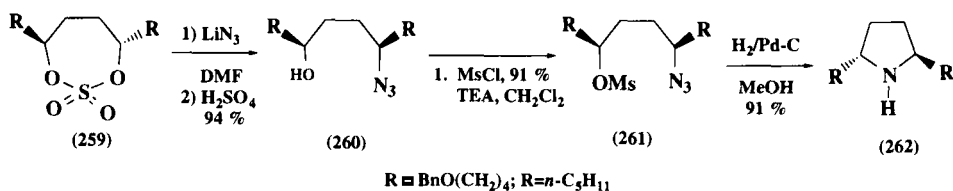
(2*R*,3*R*)- β -Hydroxyvaline **265** has been prepared by stereoselective opening of cyclic sulfate **263** with azide ion to give ethyl α -azido- β -hydroxy-4-methylpentanoate **264**, which was reduced by $\text{Pd}(\text{OH})_2/\text{H}_2-\text{CH}_3\text{OH}$ (94T9181) (Scheme 67).



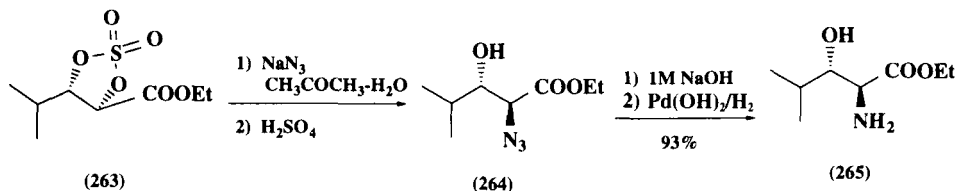
SCHEME 64



SCHEME 65

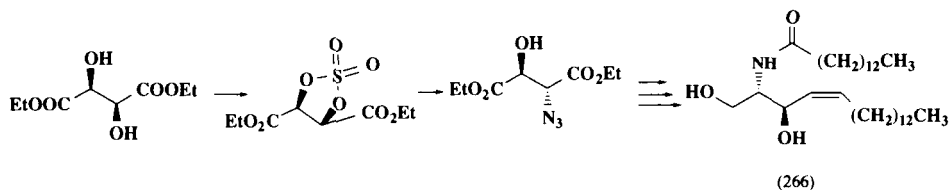


SCHEME 66



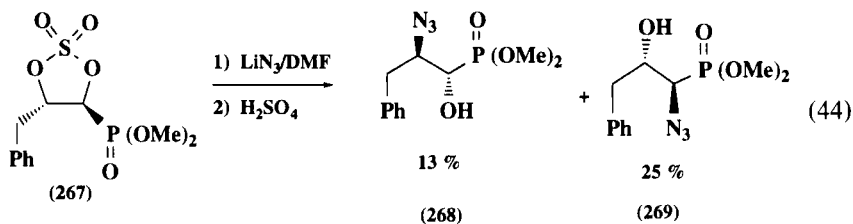
SCHEME 67

Similarly, (2S,3R,4E)-2-octadecanoylamino-4-octadecene-1,3-diol **266** has been prepared from diethyl tartrate cyclic sulfate by azide opening of the sulfate ring as shown in Scheme 68 (93LA55).

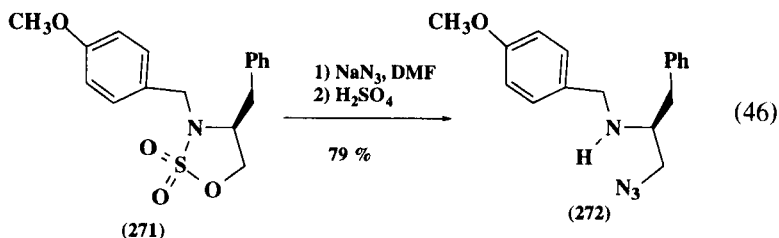
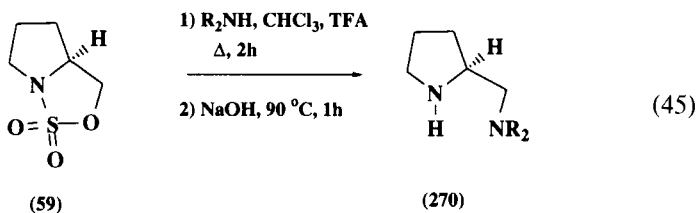


SCHEME 68

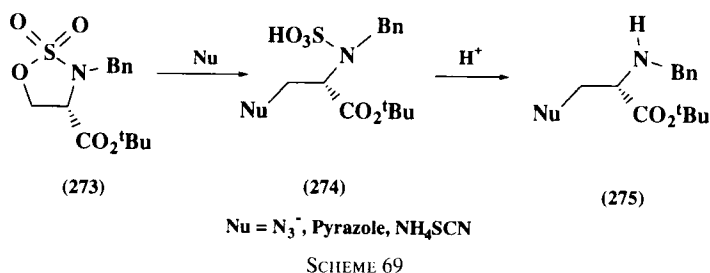
Lithium azide in DMF has also been used to ring open a cyclic sulfate derived from α,β -dihydroxyphosphonic acid derivatives. Thus, cyclic sulfate **267** gave a mixture of α -azido as well as β -azidophosphonate in 38% overall yield [Eq. (44)] (94JOC7930).



Similar to a cyclic sulfate, cyclic sulfamides **59** derived from proline or substituted ephedrine **271** can react with azide ion or an amine to give azido amine and finally diamine. Thus, opening of sulfamate **271** with sodium azide and **59** with R_2NH gave azido amine **272** (91JOC3177) and diamine **270** (90TA877) [Eqs. (45) and (46)], respectively.



Sulfamate **273** derived from serine undergoes regio- and stereoselective opening with NaN_3 in acetone–water to give 93% yield of azido amino acid **274**. Interestingly, pyrazole can also function as a nucleophile to furnish a pyrazole-substituted amino acid (Scheme 69) (89EUP324691, 89EUP325513; 92MI2). Sulfamate also undergoes ring opening with other nucleophiles such as ammonium thiocyanate (90TA881).

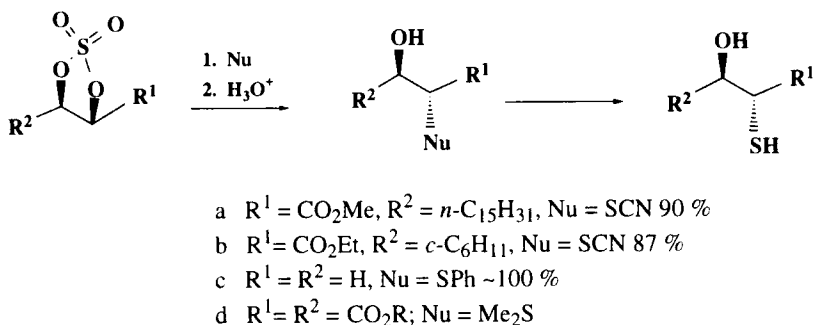


5. Sulfur Nucleophiles

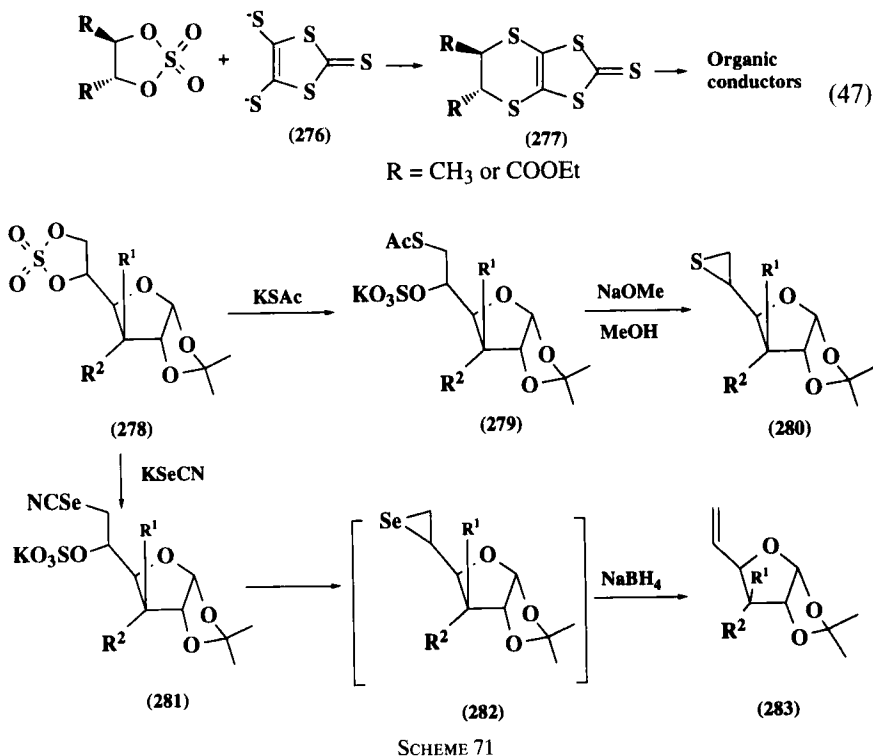
Ethylene sulfites as well as sulfates react with thiophenolate ions in a manner similar to phenolate ions (*vide supra*), but the product arising from the reaction of thiophenol with ethylene sulfate is unstable and readily hydrolyzes to give β -(phenylthio)ethanol (72JHC891). However, substituted cyclic sulfates derived from α,β -dihydroxy esters react readily with ammonium thiocyanate or thiophenolate selectively at an α -carbon atom of an ester group to give a β -hydroxy- α -thiocyano derivative or α -(phenylthio)- β -hydroxy derivative in excellent yields (88JA7538). The reaction proceeds with complete inversion at the stereogenic center, as shown in Scheme 70. Dimethyl sulfide has also been used as a nucleophile (93MI5).

Cyclic sulfates also undergo double nucleophilic displacement by dianion **276** in methanol to give a 1:1 adduct, which cyclizes to **277** on heating. Compound **277** is used in chiral organic conductors and superconductors (86HCA69; 93BCJ513; 94T11205) [Eq. (47)].

Cyclic sulfates **278** are transformed into episulfides **280** by treatment with potassium thioacetate or thiourea followed by reaction with sodium

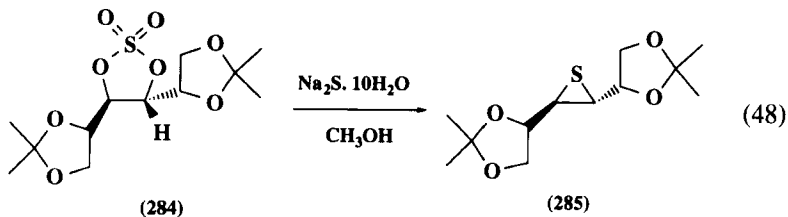


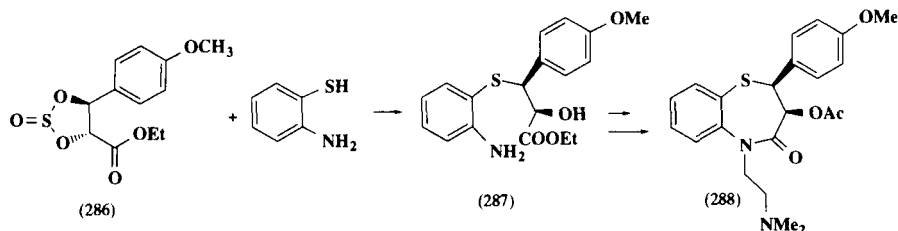
SCHEME 70



methoxide. Thus, sugar episulfides were isolated in 55–91% yield [95JC-S(CC)461]. The reaction sequence is shown in Scheme 71.

A cyclic sulfate **278** treated with potassium selenocyanate gave the expected selenirane **282**, which underwent the elimination of a selenium atom, giving rise to alkene **283** [95JCS(CC)461] (Scheme 71). Interestingly, the reaction of di-*O*-isopropylidene cyclic sulfate **284** with sodium thioacetate did not yield the corresponding episulfide **285**. However, when sodium sulfide was used as a nucleophile in boiling methanol, a 42% yield of episulfide **285** was obtained [Eq. (48)] [94JCS(CC)461].





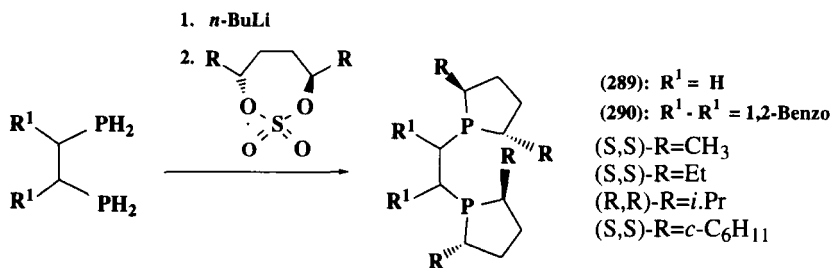
SCHEME 72

An elegant synthesis of diltiazem (**288**) by stereoselective ring opening of a cyclic sulfite with *O*-aminothiophenol has been reported. Interestingly, the nucleophilic ring opening proceeds with retention of configuration as shown in Scheme 72 to furnish predominantly 2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionate **287**, which was finally transformed into diltiazem (**288**) (95JOC5983).

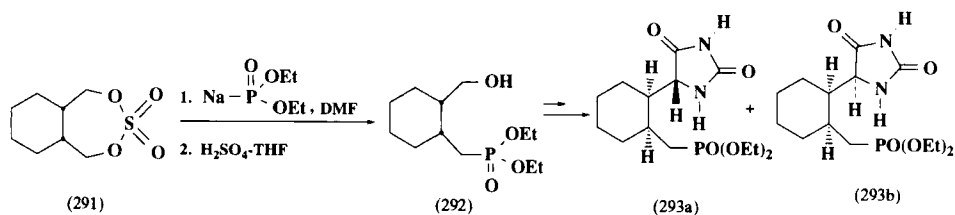
6. Phosphorus Nucleophiles

Bisphosphine chiral auxiliaries have been prepared by stereoselective double displacement of a seven-membered cyclic sulfate with 1,2-bis(phosphino)ethane in the presence of *n*-BuLi (91JA8518) (Scheme 73). Similarly, 1,2-bis(phosphino)benzene gave bisphosphine **290** (Scheme 73). These chiral auxiliaries have proved to be powerful ligands in a stereoselective hydrogenation reaction (95JA4423).

Seven-membered *meso*-cyclic sulfate **291** also undergoes ring opening with sodium diethylphosphite in DMF to give diethylphosphono alcohol **292**, which after hydrolysis (95TA3055) is finally converted into optically active hydantoins **293** (Scheme 74).



SCHEME 73

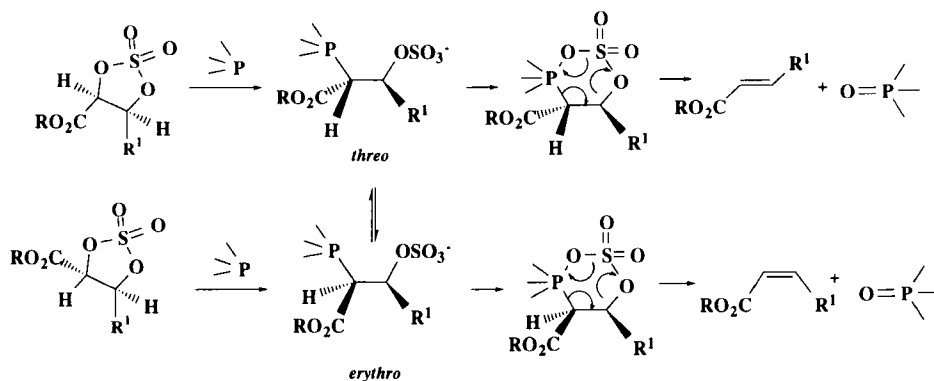


SCHEME 74

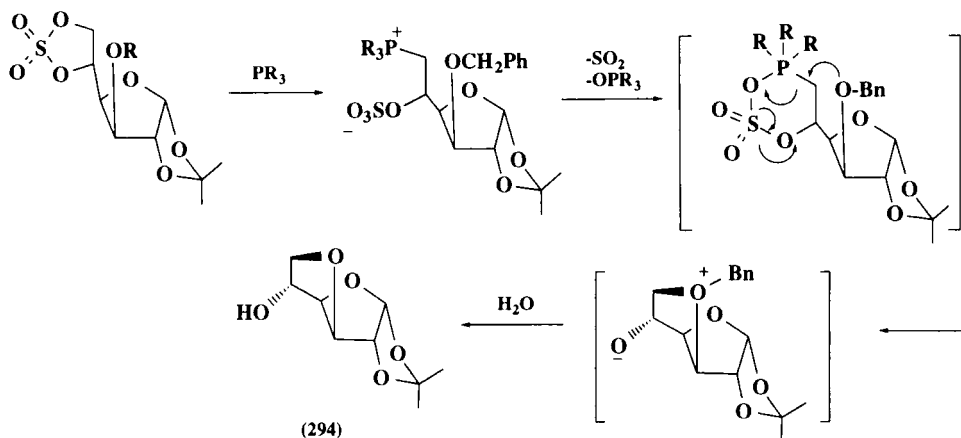
Appropriately substituted cyclic sulfates undergo an elimination reaction when treated with phosphines such as triphenylphosphine and trimethylphosphine in suitable solvents. The reaction is visualized to proceed via a phosphium sulfate salt as shown in Scheme 75. In the case of sugar-derived cyclic sulfates, anhydro sugars **294** were isolated (94SC1157) (Scheme 76).

7. Hydride Nucleophiles

Only very limited studies have been conducted using hydride as a nucleophile. The nucleophilic ring opening of a few cyclic sulfates using hydride as nucleophile has been reported (83JOC3507). Using sodium cyanoborohydride or sodium borohydride as hydride transfer agent, several cyclic sulfates have been reduced to the corresponding alcohols (88JA7538) [Eq. (49)]. For example, tartrate ester sulfate gave a 55% yield of optically pure malic ester when treated with sodium cyanoborohydride in tetrahydrofuran

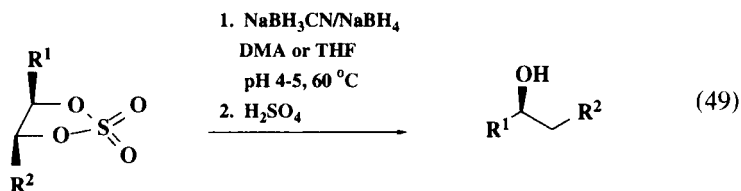


SCHEME 75

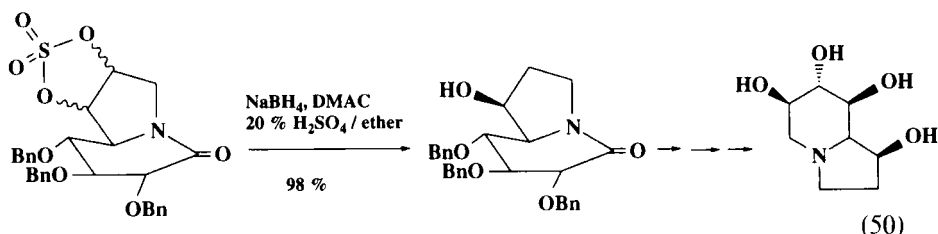


SCHEME 76

at pH 4–5 at ca. 60°C , whereas the other cyclic sulfates gave a 90% yield of β -hydroxy esters on treatment with sodium borohydride [Eq. (49)].

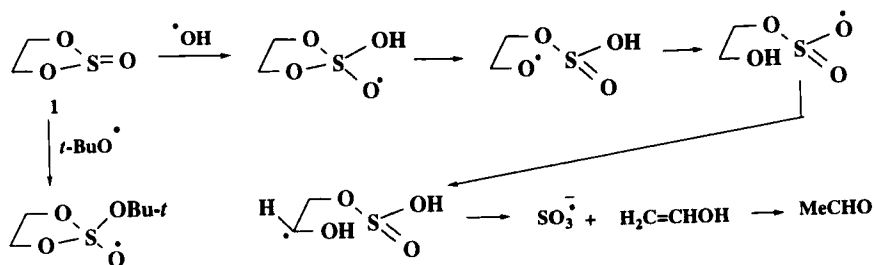


Castanospermine has been synthesized by stereoselective reduction of cyclic sulfate with sodium borohydride as shown in Eq. (50) (96TL547).

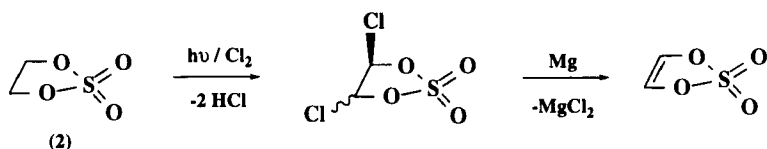


IX. Reaction with Radicals

The hydroxy radicals react with 1,3,2-dioxathiolane 2,2-dioxide to give acetaldehyde via the intermediacy of various radical species (Scheme 77),



SCHEME 77



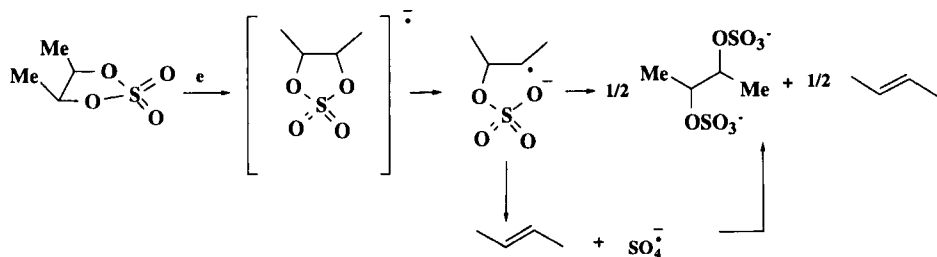
SCHEME 78

which have been detected by ESR spectroscopy after trapping with nitromethane aci anion [76JCS(P2)1040]. Similarly, *tert*-butoxyl radical attacks at the sulfur atom to yield another radical species (77JMR509).

In contrast to the oxidative cleavage of cyclic sulfites with chlorine, the photochemical chlorination of 1,3,2-dioxathiolane 2,2-dioxide gave a 4,5-dichloro derivative, which was formed via a radical process. Subsequent dechlorination of the dichloro compound with magnesium in refluxing tetrahydrofuran gave 1,3,2-dioxathiole 2,2-dioxide (Scheme 78) (68JA2970).

X. Electrochemical Reduction of Cyclic Sulfates

Cyclic sulfates of several 1,2-, 1,3-, and 1,4-diols have been reduced by a stepwise single-electron transfer reaction using cyclic voltammetry (84BCJ3160). The interesting mechanism of reduction is outlined in Scheme 79; the cyclic sulfate undergoes disproportionation to give an olefin and a bisulfate ion (83MI2).



SCHEME 79

XI. Application in Research and Industry

The possible application of cyclic sulfites and cyclic sulfates has already been emphasized (*vide supra*). Cyclic sulfate derivatives of chiral diols have also been used for stereochemical assignment of diols by a chiroptical method (74JOC2073). Ethylene sulfite has been patented as an alkylating agent in organic synthesis [52BRP670159; 81JAP(K)81/152461; 82JAP(K)57/169463; 83JAP(K)58/103349; 86MIP1; 87JAP(K)62/36372; 89EUP298399, 89EUP324691; 90EUP343053], as a spinning solvent for polyacrylonitrile (55USP2706674; 56USP2752318), as starting material for the production of polyesters (57BRP781169) or polyurethanes (62BEP-610763; 65BEP659395), and as a scrubbing liquid for removal of hydrogen sulfide from gaseous mixtures (62BRP902256). Other applications of ethylene sulfites are as washing liquids for purification of polyalkenes (62BRP903077), in detergents (62GEP1124962), in a photographic emulsion for hardening of gelatin used in photographic materials (90USP 4877724), and in textile industries (66GEP1223397). Potential uses of cyclic sulfites as an aminoplastic molding composition, as vulcanization accelerators (64FRP1379555), as antioxidants (89EUP298399), as a component of a hair dyeing agent, and as a preservative for black-and-white developers (73USP3713826) are also known. They are also used as preservatives for lubricating oil additives and foods (93EUP552651). The cyclic sulfite derive from L-ascorbic acid also acts as a food additive and antioxidant in the fermentation of wine (89EUP298399; 91MI1).

Anthraquinone dyes with a cyclic sulfite ester group may be used for dyeing polyester fibers. Cyclic sulfites of several 1,2-diols have been used as pH regulators in the dyeing process of polyamide and merino wool (88GEP3704125). Some of the colors of the dyes have been improved by the addition of a cyclic sulfite (82EUP55694). Ethylene sulfate is used to introduce substituents into nitrogen heterocycles, especially in cyanine dyes (58GEP1028718). Fluorinated derivatives are useful in the treatment of textiles such as cotton to impart wash-and-wear characteristics (62USP3055913). Cyclic sulfate is also employed in making polymers with high-impact plastic and rubber goods, prepared by coupling a lithium-initiated living polymer (64USP3154526). Substituted cyclic sulfites are also used in the manufacture of amphoteric surfactants and polymer coagulants [86JAP(K)60/228472]. A polymer of methacrylate and ethylene sulfites has been employed as an antistatic coating material (84MI1). A copolymer of cyanoacrylate monomer and cyclic sulfate has been used to improve the thermal stability of the polymer and thus act as heat stabilizer (94EUP579476). Cyclic sulfites and cyclic sulfates are also used as cross-linking agents in copolymerization [94JAP(K)06/345977]. Cyclic sulfites are

also employed as deliming agents for hides (87GEP3527013). Recently, cyclic sulfites have found use in high-energy lithium batteries as cosolvents (82FRP2490020; 88BRP2202670) and as electrolytes in certain lithium cells [87JAP(K)62/108474; 88M649]. Some cyclic sulfites are used as solvent mixtures for battery electrolyte [91MI2; 94JAP(K)06/302336] rechargeable lithium cells (88MI2) and also as electrolytes in electrochromic light-controlling devices [88JAP(K)63/59590]. Chiral organic conductors and superconductors are being developed from homochiral cyclic sulfates derived from optically active butane-2,3-diols (86HCA69). Some cyclic sulfates are also used to synthesize unnatural sugars such as 6-deoxy-D-mannoheptopyranoside (92MI1) and in the synthesis of optically active nipradiol [93JAP(K)05/70452] virucidal (91EUP432694) and the optically active ceramide of GM₁ ganglioside (93LA55). Cyclic sulfite and cyclic sulfates with proper substituents are also used as calcium-dependent neutral proteases and other enzyme inhibitors (91MIP1). Biodegradable polymers have been prepared by copolymerization of the cyclic sulfate derived from tartronic acid (87MI1). Ethylene sulfite is also employed in making polymers with high-impact plastic and rubber goods, prepared by coupling of a lithium-initiated living polymer (81USP4301258). Endosulfan is a polychlorinated cyclic sulfite used as an insecticide (61USP2983732).

XII. Biological Activities

Five-membered cyclic sulfites and sulfates are toxic because of their potential bioalkylating properties. Ethylene sulfate, which is more toxic than dimethyl sulfate, induces local malignant tumors after subcutaneous injection and has proved to be a weak mutagen in both *in vitro* and *in vivo* studies (74MI1; 77MI1; 94JOC520). Recently, ethylene sulfate has been tested in frogs, and it has been found to selectively destroy Leydig cells and to affect the level of androgens and sperm (90MI2). Antimicrobial properties are present in the cyclic sulfite derivative of erythromycin (88EUP273375). Similarly, certain imidazole-substituted cyclic sulfites are active antifungal agents (90EUP399901). Cyclic sulfites of monohydric as well as polyhydric alcohols are used as antihypertensive or antithrombotic agents (83EUP113235). Recently, some cyclic sulfite and sulfate derivatives of suitably substituted sugars have been used as anticonvulsant agents (93USP5242942, 93USP5258402), and eight-membered cyclic sulfamides have been developed as antiviral agents (93MIP1). Cyclic sulfates have also been involved in the inhibition of thiol protease [94JAP(K)06/199831].

XIII. Conclusion

The chemistry of cyclic sulfites and cyclic sulfates, although not new, has only recently begun to be explored by synthetic chemists. In recent years, several synthetic applications of cyclic sulfites and sulfates have appeared. In this chapter, attempts have been made to draw the attention of synthetic chemists to the great potential hidden in this neglected class of useful organic compounds, which at present is accessible in homochiral form via the recently discovered asymmetric dihydroxylation of alkenes.

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Methylpyridines and Other Methylazines as Precursors to Bicycles and Polycycles

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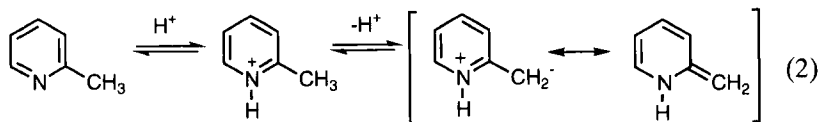
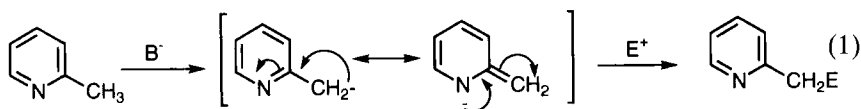
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I. Introduction

Methyl groups attached to aromatic heterocyclic rings may behave very differently than methyl substituents on aromatic hydrocarbons. For example, methyl groups on π -deficient six-membered heterocyclic systems are more reactive toward bases and/or electrophiles than are methyl groups attached to a benzene ring. Substituents in the β -position are more reactive as a consequence of the overall electron deficiency of the ring system; substituents α and γ to the ring nitrogen are significantly still more reactive, especially in processes that proceed via base-catalyzed deprotonation from the methyl substituent, as the resulting anions are resonance stabilized, as in Eq. (1).

As expected, methyl groups on heterocyclic systems where a ring nitrogen is formally positively charged, i.e., in *N*-oxides and pyridinium salts, are more reactive than those in uncharged systems. Thus, acid-catalyzed reactions are also possible, as in Eq. (2). The effect of other substituent groups



on the reactivity of the methyl substituents is also generally predictable; for example, electron-withdrawing groups further increase the reactivity, i.e., facilitate proton removal from methyl groups ortho and para to them. Also, additional heteroatoms increase the reactivity of the methyl group: methyl groups attached to pyrimidine, pyrazine, and pyridazine are more reactive than those on pyridine.

This review surveys reactions in which the special properties of these types of methyl groups are used in the construction of fused rings, usually by routes in which the deprotonated methyl group reacts with an adjacent substituent directly, or more often by reaction with another reagent to give an intermediate, which in turn cyclizes via an adjacent substituent. Reactions in which cyclization occurs via attack at a ring nitrogen or carbon are also included. The survey is intended to include representative examples of the various types of reaction, rather than to be exhaustive. It is also restricted to reactions that are, or could be, "one-pot." The reactions are classified in terms of the other ring substituent (or ring atom) involved.

Although in principle analogous reactions involving homologs should be possible, very few have been reported. However, one or two examples have been included.

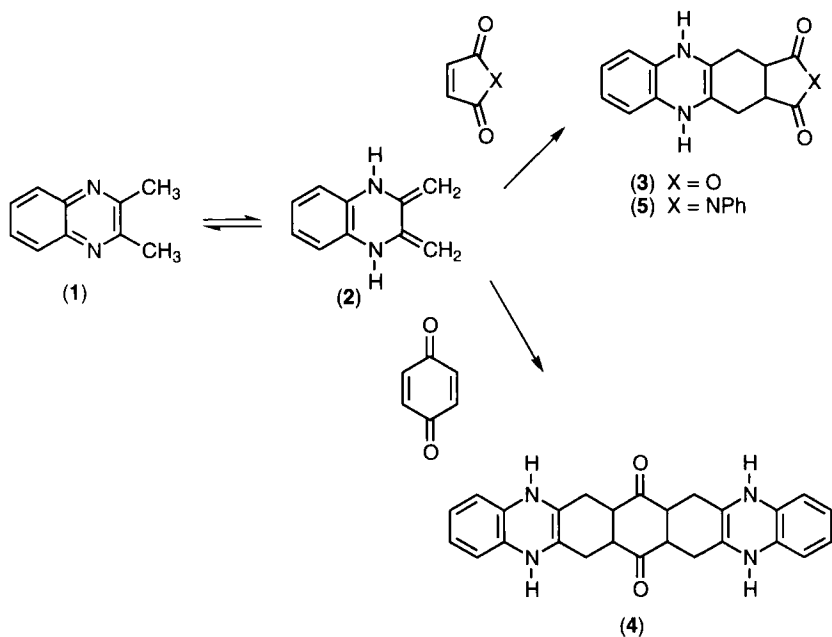
II. Methyl and Alkyl

A. REACTION WITH DIENOPHILES

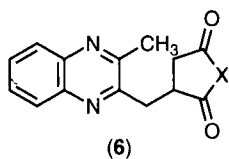
The reaction of 2,3-dimethylquinoxaline (**1**) with maleic anhydride and with benzoquinone gave 1:1 (**3**) and 1:2 adducts (**4**), respectively (43JCS654), and an analogous reaction with *N*-phenylmaleimide gave the 1:1 adduct (**5**) (55JA1828). These reactions were rationalized in terms of an equilibrium between **1** and its tautomer (**2**), which undergoes [4 + 2] cycloaddition with the dienophiles, as shown in Scheme 1. However, these reactions were repeated by Bird and Cheeseman (62JCS3037) and by Taylor and Hand (63JA770), who isolated uncyclized intermediates (**6**) in addition to **3**. The reactions may therefore proceed stepwise, possibly via an initial Michael addition.

B. VIA α,α' -DICHLORINATION

Photochlorination of the lutidines (**7**, **8**) by *N*-chlorosuccinimide gave the unstable intermediates (**9**), which were converted into the dihydrothienopyridines (**10**) on treatment with sodium sulfide (72JHC843; 73USP3709894) (Scheme 2).

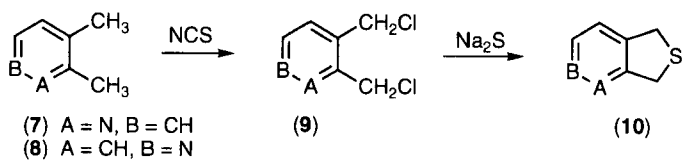


SCHEME 1

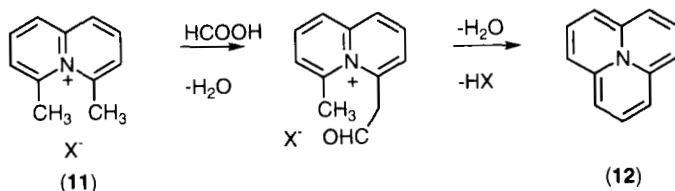


C. REACTION WITH FORMIC ACID

In a reaction involving *peri*-methyl groups, the 4,6-dimethylquinolizinium salt (**11**) reacted with formic acid in the presence of acid to afford cycl[3.3]azine (**12**) (63JOC393) (Scheme 3).



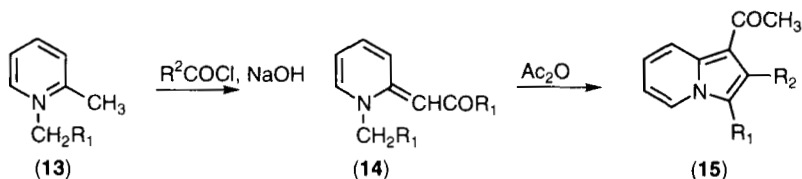
SCHEME 2



SCHEME 3

D. REACTIONS OF *N*-ALKYL-2-METHYLPYRIDINIUM SALTS

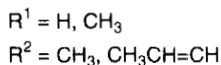
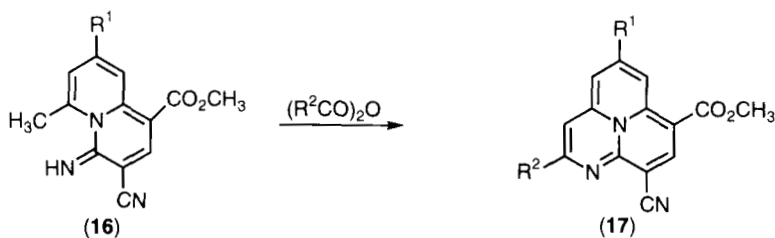
In a process akin to the reactions via azinium salts described in Section XIII,A, *N*-substituted methylpyridinium salts (**13**) were converted into 2-alkylidenedihydropyridines (**14**), and thence into indolizines (**15**), as shown in Scheme 4 [65JCS(CC)151; 67JCS(C)983]. It seems likely that this sequence could be performed as a "one-pot" process (72CB2344), especially for the case where $R^1 = \text{Me}$.



SCHEME 4

III. Methyl and Imine

The reaction of the methyl group and the *peri*-imino group in methyl 3-cyano-4-imino-6-methyl-4*H*-quinolizine-1-carboxylates (**16**) (74CPB1424; 75YZ1431) with carboxylic anhydrides afforded the azacyclo[3,3,3]azines (**17**) (75CPB2759), as shown in Scheme 5.



SCHEME 5

IV. Methyl and Cyano

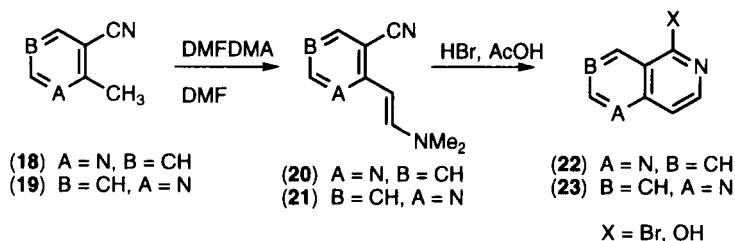
A. REACTION WITH DIMETHYLFORMAMIDE DIMETHYLACETAL

Methyl groups vicinal to cyano substituents in azines readily condense with dimethylformamide dimethylacetal (DMFDMA) to yield dimethyl-aminoethenyl intermediates, which cyclize to give condensed pyridines in both acid and alkaline media. For example, reaction of the cyanopicolines (**18**, **19**) with DMFDMA gives the enamines (**20**, **21**), which are readily converted into the pyridopyridines (**22**, **23**) on heating with HBr–AcOH (78JOC4878), Scheme 6.

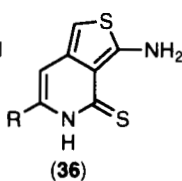
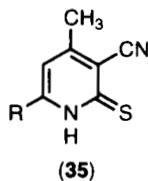
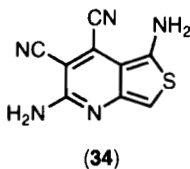
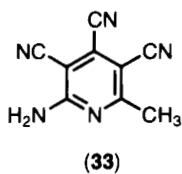
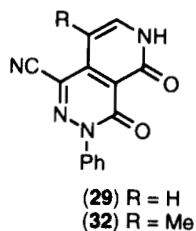
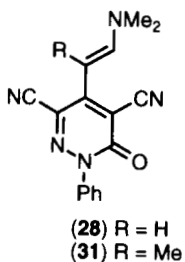
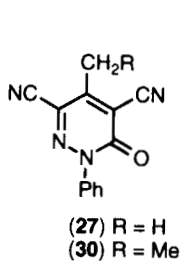
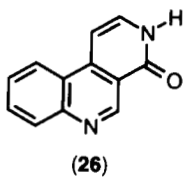
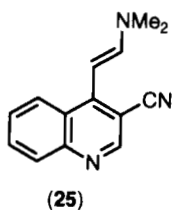
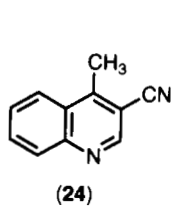
The cyanoquinaldine (**24**) similarly gives the pyrido[3,4-*c*]quinoline (**26**) via intermediate (**25**) (89AP511), and this type of reaction has been extended to the synthesis of a pyridopyridazine (**29**) from the dicyanopyridazinone (**27**) via the enamine (**28**); it is noteworthy that only the regioisomer shown (**29**) was obtained (isolated as the corresponding carboxylic acid) [95JCR(M)2924, 95JCR(S)488]. This sequence has also been applied to the homologs (**30**, **31**, **32**) (95T12745).

B. REACTION WITH SULFUR

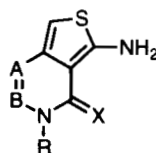
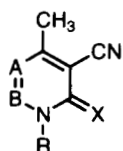
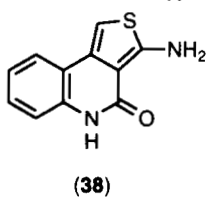
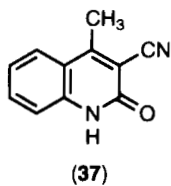
Elnagdi *et al.* reported the preparation of thieno[4,3-*b*]pyridine (**34**) (90LA1215), thieno[3,4-*c*]pyridine (**36**) (90LA1215), thieno[3,4-*c*]quinolinone (**38**), and thienodiazines (**41**, **42**) [89LA1255; 90JCR(S)148; 94TH1] by the reaction of the methyl and cyano groups of cyanopyridines (**33**, **35**), cyanoquinolinone (**37**), and cyanodiazines (**39**, **40**), respectively, with elemental sulfur in the presence of base. The products were found to be reactive as dienes, undergoing cycloaddition with electron-poor olefins and extrusion of sulfur to give benzoazines [93JCR(S)130]. [Note that the structure previously reported for **42** (92G503) has been shown to be incorrect [96MI2].]



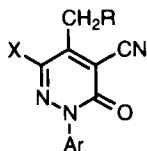
SCHEME 6



R = Me, Ph



This is another of the few cases where the reactions of methyl azines have been extended to homologs; the ethyl- and benzylpyridazines (**43–45**) were found to react in a similar way (92G503; 94SL27; 95T12745).



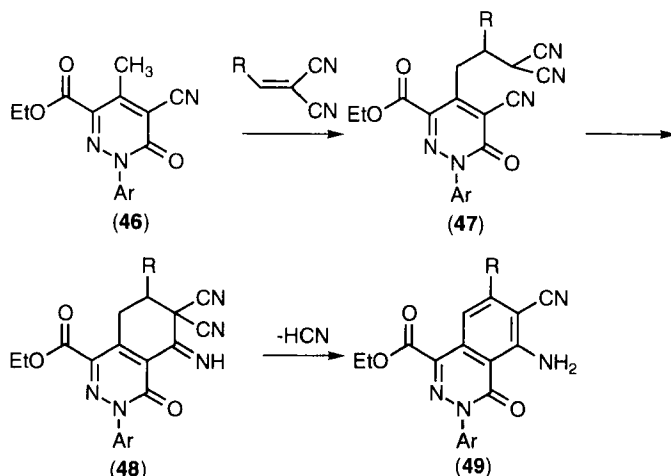
(**43**) R = Me, X = CO₂Me

(**44**) R = Me, X = CN

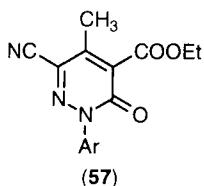
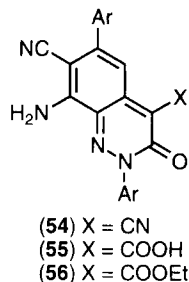
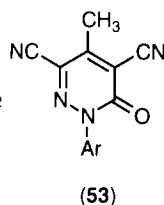
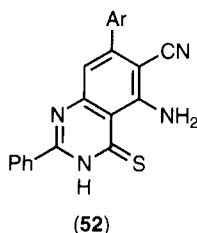
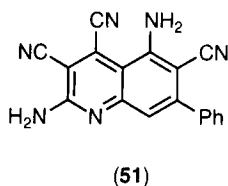
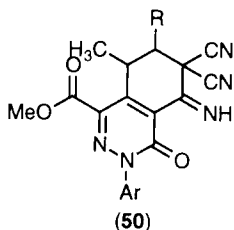
(**45**) R = Ph, X = CN

C. REACTIONS WITH ALKYLIDENEMALONONITRILE DERIVATIVES

Elnagdi *et al.* [88LA1005; 90LA1215, 90ZN(B)389; 92JPR723; 93JCR(S)130] have extensively investigated the reactivity of alkylazinylnitriles with alkylidenemalononitrile derivatives; their work has been surveyed (94SL27). The type of reaction may be illustrated by the example shown in Scheme 7 (88LA1005), in which reaction of the pyridazinones (**46**) with benzylidenemalononitriles gives the phthalazines (**49**). The Michael adducts (**47**) and the tetrahydrophthalazines (**48**) are proposed intermediates. The tetrahydrophthalazines (**50**) have been obtained from analogous reactions of the homologs (**43**) (95T12745).



SCHEME 7

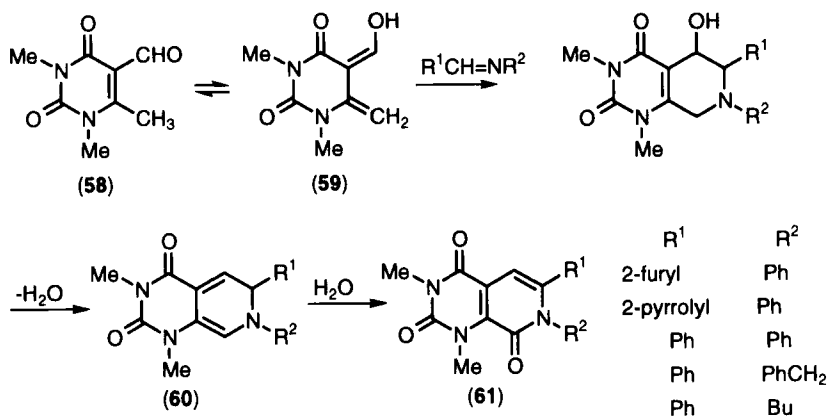


Other substrates for reactions of this type include the pentasubstituted pyridine (33), which gives the quinoline (51) with methylidenemalononitrile, prepared *in situ* (90LA1215); the pyrimidinethione (39), which gives the quinazoline (52) (90LA1215); and the dicyanopyridazinone (53), which gives the cinnoline (54) (89T3597). In the last case, the regiochemistry was proved by establishing the identity of the corresponding acid (55) with the compound (56) derived from the ester (57) [90ZN(B)389].

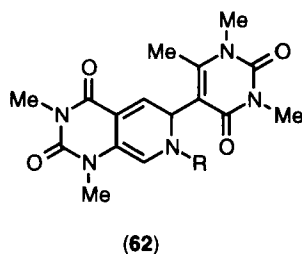
V. Methyl and Carbonyl

A. METHYL AND FORMYL

It is reported that the formylpyrimidinedione (58) reacts with Schiff bases to yield the dihydropyrido[3,4-*d*]pyrimidinediones (60), which are partially hydrolyzed to the triones (61) on workup (89MI1). A likely mechanism (Scheme 8) involves [4 + 2] cycloaddition of the imine to the tautomer (59), followed by dehydration. The trione (61, R¹ = 2-furyl, R² = Ph) was assigned the structure shown, rather than the regioisomer, which might



SCHEME 8



have been predicted, on the basis of the absence of any nOe effect between an *N*-methyl group and the ring proton.

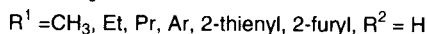
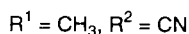
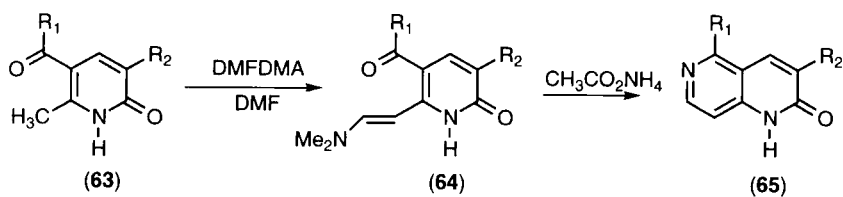
Reaction of two equivalents of the same starting material (58) with amines is claimed to give the unexpected pyridopyrimidines (62), on the basis of NMR spectroscopy, including nOe measurements (88JHC205).

B. METHYL AND KETONE

1. Methyl and Acyl

a. *Via Reaction with DMFDMA.* Treatment of the acylpyridinones (63) with DMFDMA gives enamines (64), which on treatment with aqueous ammonium acetate cyclize to give 1,6-naphthyridines (65) (90JHC2085) (Scheme 9).

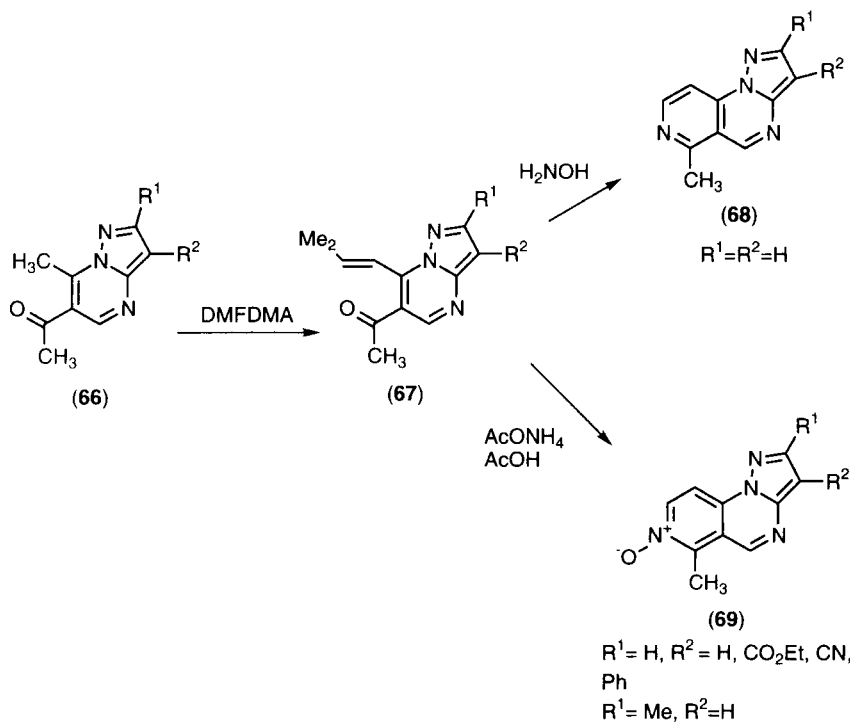
The conversion of the pyrazolopyrimidine derivatives (66) into the enamines (67) by reaction with DMFDMA, and cyclization to the pyrazolo [1,5-*a*]pyrido[3,4-*e*]pyrimidines (68) is analogous (90H1141). In this case,



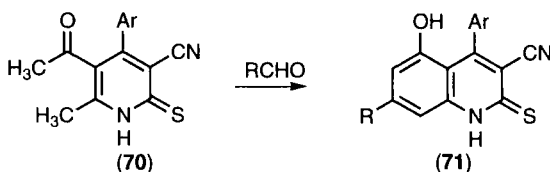
SCHEME 9

reaction with hydroxylamine in place of ammonium acetate gave the pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine-7-oxide (69) (90H1635) (Scheme 10).

b. *Reaction with Aldehydes.* Condensation of the acylpyridinethiones (70) with aromatic aldehydes or formaldehyde gave the quinolines (71) (Scheme 11) (91CCC2175).



SCHEME 10



SCHEME 11

2. Methyl and *N*-Phenacyl

The *N*-phenacylquinazolinone (**72**) cyclizes in aqueous alkali to give the intermediate (**73**), which isomerizes on recrystallization to the pyrrolo[2,3-*a*]quinazolinone (**74**), Scheme 12 (86T4481).

C. METHYL AND CARBOXYLIC ACID

1. With Thionyl Chloride

The thienopyridines (**77**) are obtained by reaction of the 4-methylnicotinic acids (**75**) with thionyl chloride, followed by hydrolysis of the unstable dichloro intermediates (**76**) (69JOC247) (Scheme 13).

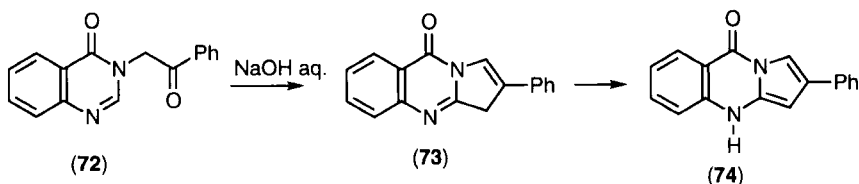
2. With Oxalyl Chloride

The same starting half ester (**75**, R = COOMe) on reaction with oxalyl chloride followed by methanolysis gives the pyrano[3,4-*c*]pyridine (**78**) (69JOC247) (Scheme 13).

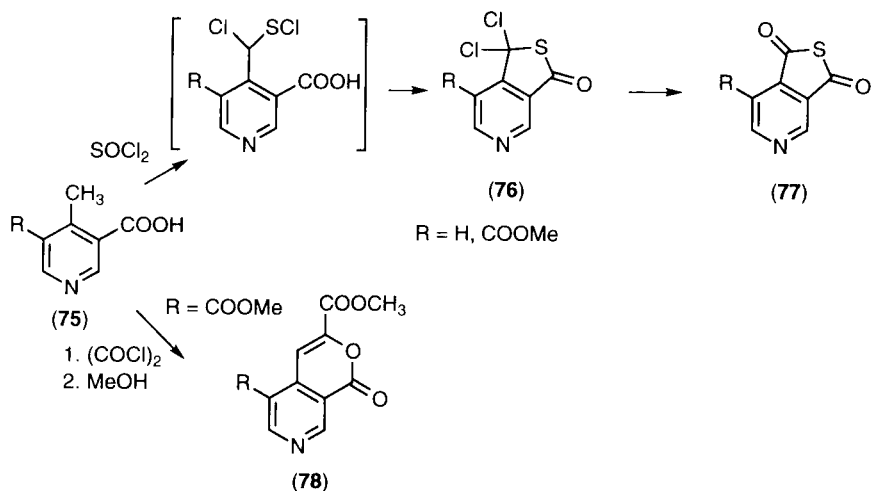
3. With Vilsmeier Reagent

Reactions of the methylpyridinecarboxylic acids (**79**, **80**) with phosphorus oxychloride and DMF give the formylnaphthyridinones (**83**, **84**); the intermediates (**81**) and (**82**), shown in Scheme 14, are postulated (83TL4607).

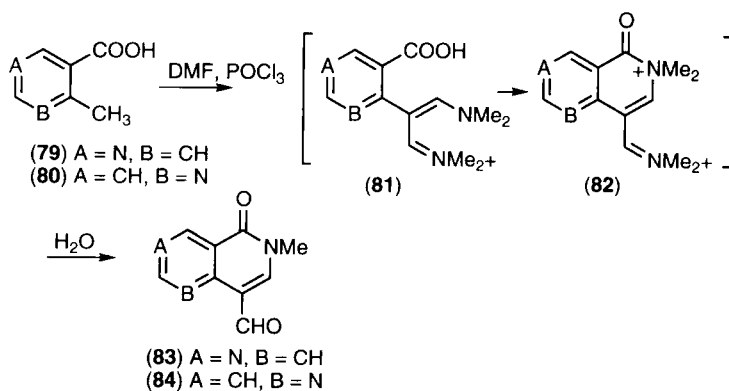
Similarly, reactions with Vilsmeier reagent of the pyridinedicarboxylic acids (**85**), the quinolinecarboxylic acids (**86**), and the quinoxalinecarboxylic acids (**87**) gave the tricyclic products (**88**, **89**, **90**), respectively (83TL4607).



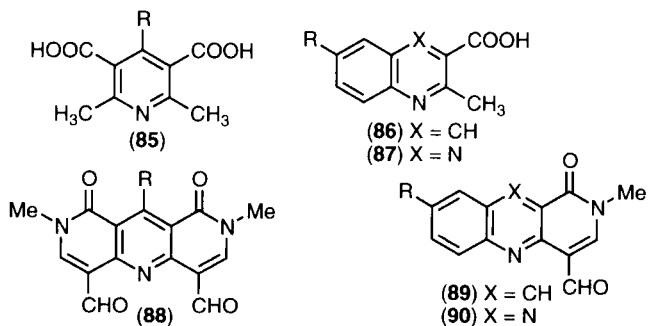
SCHEME 12



SCHEME 13



SCHEME 14



D. METHYL AND CARBOXYLIC ESTER

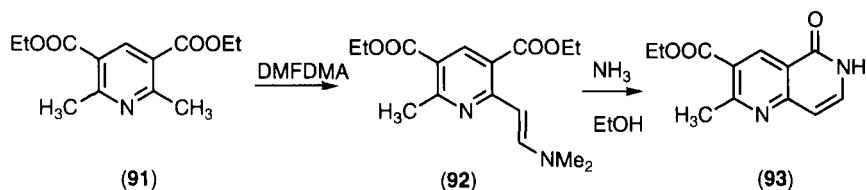
1. *Via DMFDMA*

A methyl group in the diester (**91**) condenses readily with DMFDMA to give the enamine (**92**), which cyclizes on treatment with ammonia to give the 1,6-naphthyridinone (**93**), Scheme 15 [86JCS(P1)753].

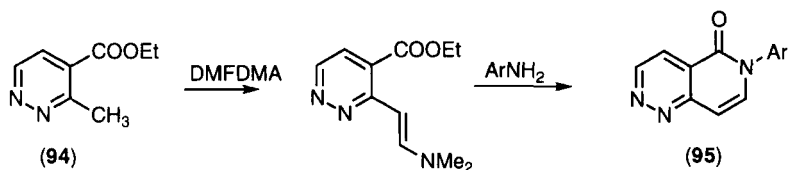
The syntheses of pyridopyridazines (**95**) and (**97**) from the pyridazinecarboxylates (**94**) and (**96**), shown in Schemes 16 (91JHC1043) and 17 [95JCR(M)2924, 95JCR(S)488], are analogous, except for the use of amines rather than ammonia in the second step.

2. *With Carbon Disulfide*

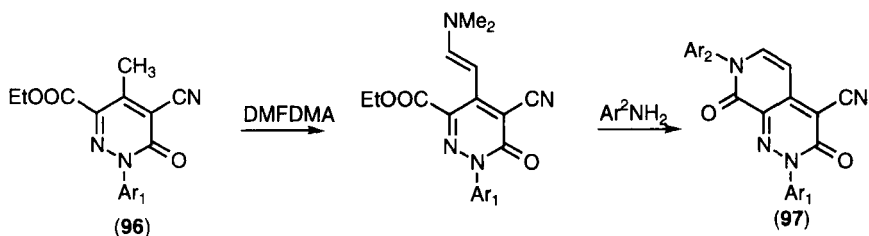
On reaction with carbon disulfide in the presence of base, followed by iodomethane, the pyridazine (**96**, $\text{Ar}^1 = \text{Ph}$) gives the thiopyrano



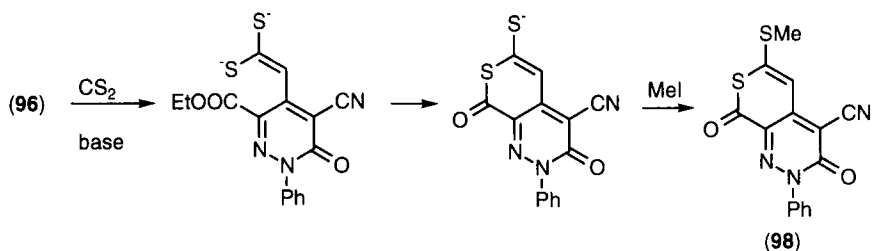
SCHEME 15



SCHEME 16



SCHEME 17



SCHEME 18

[3,4-c]pyridazine (98), presumably by the route outlined in Scheme 18 [95JCR(M)2924, 95JCR(S)488]. Preliminary experiments (94TH1) suggest that this type of cyclization can also be applied to other ring systems.

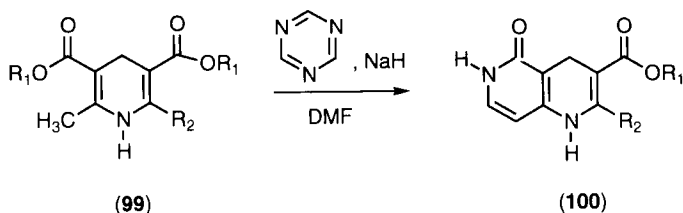
3. With 1,3,5-Triazine

Reactions of dihydropyridinedicarboxylic esters (99) with 1,3,5-triazine in the presence of base gives dihydronaphthyridinones (100) as shown in Scheme 19 (86S859). (It may be noted that the cyclization step of Scheme 15 has also been achieved, and in better yield, by the use of 1,3,5-triazine in the presence of base [86JCS(P1)753].)

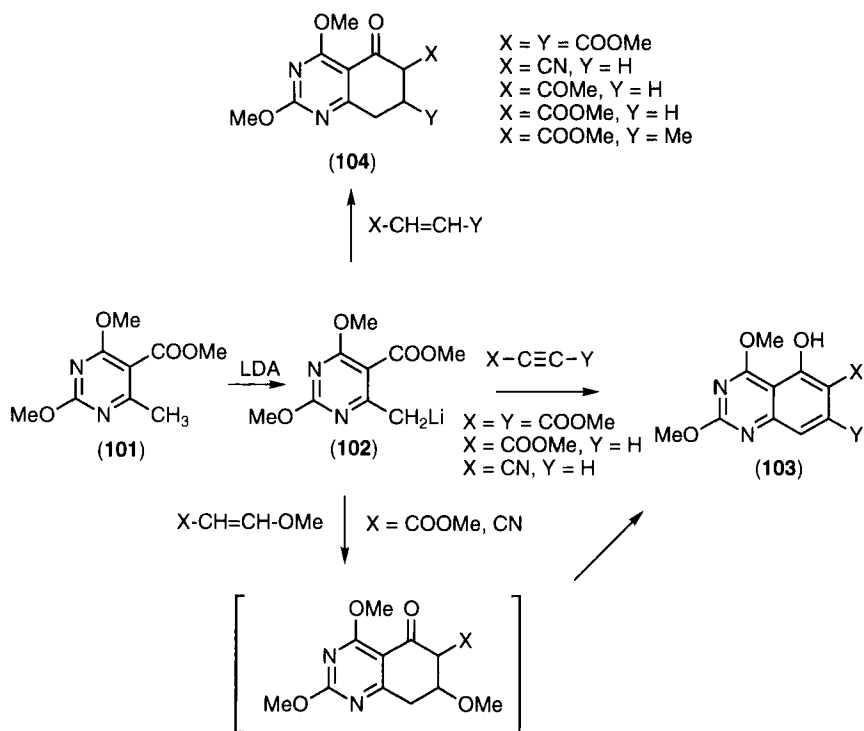
4. Reaction with Acetylenic and Olefinic Compounds

Lithiation of methyl 2,4-dimethoxy-6-methylpyrimidine-5-carboxylate (101) with lithium diisopropylamide (LDA) at -70° gives the intermediate (102). This reacts *in situ* with electron-poor acetylenes or olefins to give quinazolines 103 or 104, respectively (Scheme 20) (92JHC911).

The aromatic compounds (103) are also formed by reaction of the lithiated intermediate (102) with methoxyacrylonitrile or methoxyacrylates followed by elimination, as shown in Scheme 20 (92JHC911).



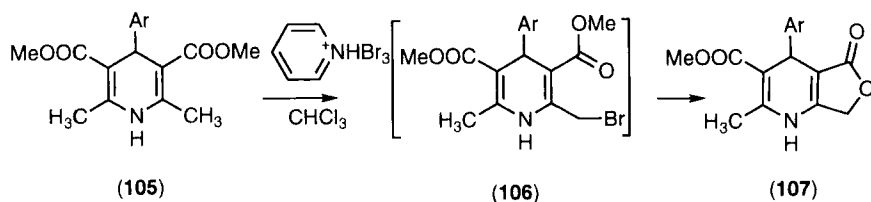
SCHEME 19



SCHEME 20

5. Via Bromination

Treatment of the dihydropyridine diester (105) with pyridinium bromide perbromide in chloroform give the lactone (107), via the unstable brominated intermediate (106) (Scheme 21) (84S617; 90TL1479).



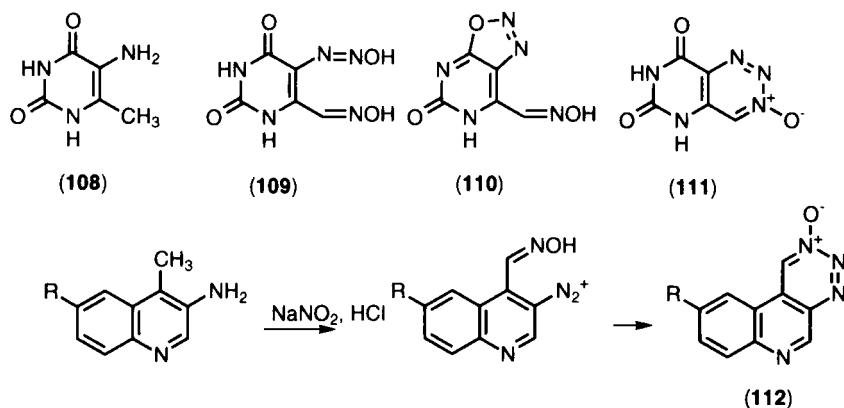
SCHEME 21

VI. Methyl and Amino

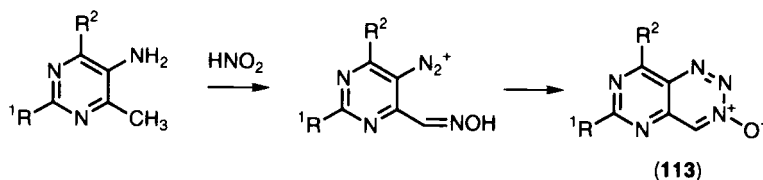
A. REACTIONS WITH NITROUS ACID

Reactions with nitrous acid of compounds with amino groups adjacent to activated methyl groups, leading to fused 1,2,3-triazine-*N*-oxides, have a long history. More than a century ago, the reaction of 5-amino-6-methyluracil (**108**) with nitrous acid was reported by Behrend [1888LA(245)213], who formulated the product as **109**. The product was later formulated as the oxime (**110**) (52JCS3448; 54JCS4116), but is now believed to be the pyrimido-1,2,3-triazine-*N*-oxide (**111**) [63JOC1329; 70JHC405]; the originally proposed structure (**109**) (or a diazonium ion equivalent, as depicted in Schemes 22 and 23) may well be an intermediate.

Other examples of this type of reaction, giving 1,2,3-triazino[4,5-*c*]quinolines (**112**) (53JCS1915) and pyrimido[4,5-*d*]1,2,3-triazines (**113**) [84JCS(P1)1471], are shown in Schemes 22 and 23, respectively. An alternative mode of cyclization gives a fused pyrazole ring [96JCS(CC)2711].



SCHEME 22



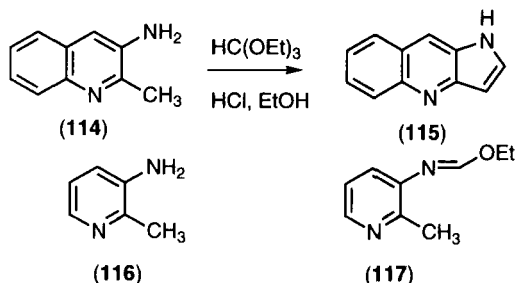
SCHEME 23

B. REACTIONS WITH FORMYLATING REAGENTS

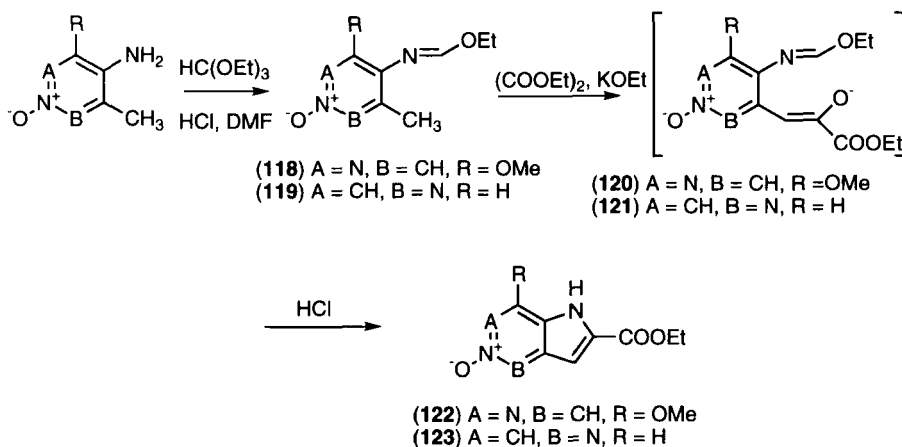
1. With Triethyl Orthoformate

The reaction of 3-amino-2-methylquinoline (**114**) with triethyl orthoformate in the presence of an acid catalyst gives pyrrolo[3,2-*b*]quinoline (**115**) [76JCS(P1)2121] (Scheme 24), although an analogous reaction of 3-amino-2-methylpyridine (**116**) gave only the uncyclized product (**117**) (65JOC2531).

A related type of reaction is shown in Scheme 25. In this case, the anions derived from the intermediates (**118**, **119**) react with diethyl oxalate to give presumed intermediates such as **120** and **121**, which on acidification cyclize to give the pyrrolopyridazine-*N*-oxides (**122**, **123**) (73JHC551, 73JHC807).



SCHEME 24



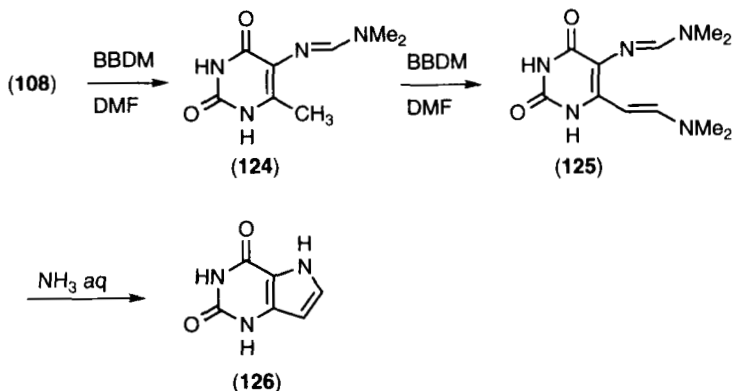
SCHEME 25

2. With *tert*-Butoxybis(dimethylamino)methane

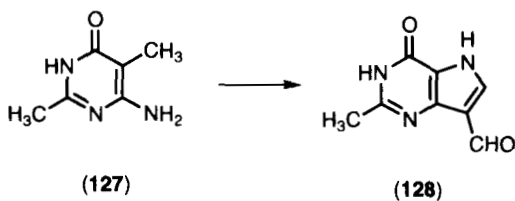
Treatment of 5-amino-6-methyluracil (**108**) with *tert*-butoxybis(dimethylamino)methane (BBDM) in hot DMF gives the amidine (**124**), which with additional BBDM in hot DMF gives the enamine (**125**). Cyclization of the latter occurs on treatment with ammonium hydroxide to give the pyrrolo[3,2-*d*]pyrimidine (**126**) (a deazapurine) as shown in Scheme 26 (78JOC2536).

3. With Vilsmeier Reagent

The pyrrolo[2,3-*d*]pyrimidine (**128**) was obtained in 67% yield by the reaction of the pyrimidinone (**127**) with phosphorus oxychloride in DMF (77CHE1338), as shown in Scheme 27. An analogous reaction of the quina-zolinone (**129**) with an excess of thionyl chloride in DMF gives the pyrrolo[2,3-*d*]quinazolinone (**130**) in good yield (73IJC532).



SCHEME 26



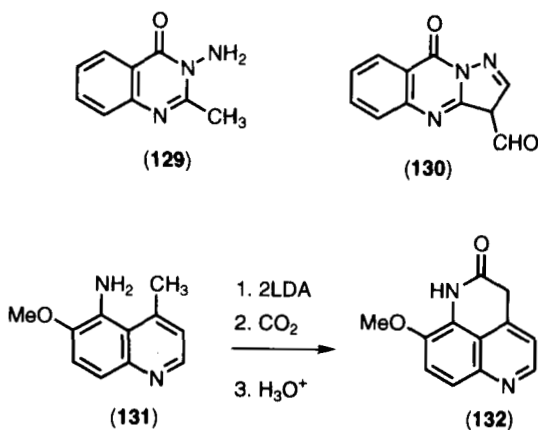
SCHEME 27

C. BY CARBOXYLATION

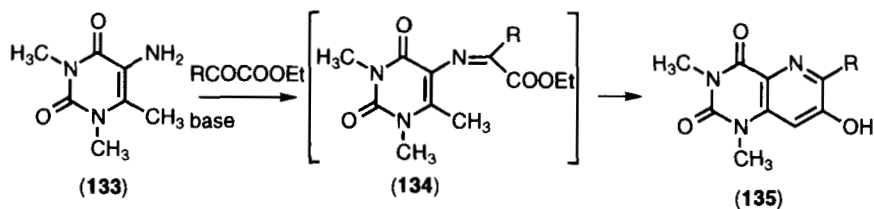
In a cyclization involving substituents in *peri* positions, carboxylation of the "dianion" from reaction of the quinoline (131) with two equivalents of LDA gives the benzo[*i,j*]-2,7-naphthyridine (132), as shown in Scheme 28 (82H2089).

D. WITH α -OXOESTERS

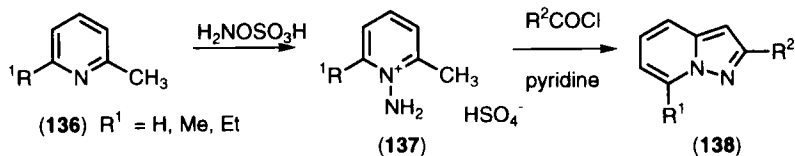
The pyrido[3,2-*d*]pyrimidine (135) was prepared by condensation of the pyrimidinedione (133) with an α -oxoester such as methyl pyruvate or ethyl mesoxalate, or with diethyl oxalate, in the presence of a base. Presumably the reaction involves initial condensation to give the imine (134) as shown in Scheme 29 (57CB728) (cf. Section VIII).



SCHEME 28



SCHEME 29



SCHEME 30

E. WITH ACYL CHLORIDES

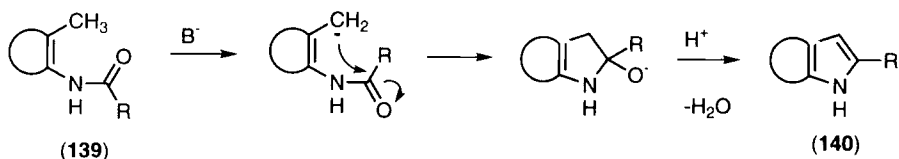
Pyrazolo[1,2-*a*]pyridine derivatives (**138**) are prepared by acylation of 2-methyl-1-aminopyridinium salts (**137**) (68JOC3766); the starting materials are obtained by amination of 2-methylpyridines (**136**) with hydroxylamine-*O*-sulfonic acid (59CB2521) (Scheme 30).

VII. Methyl and *N*-Acylamino

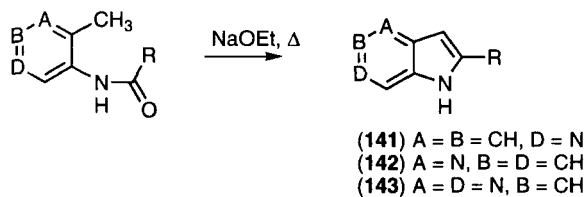
A. BASE-INDUCED CYCLIZATION

Cyclization of vicinal alkyl acylamines (**139**) induced by strong bases [the Madelung reaction and its modifications (68AHC27)] is a versatile method for preparing fused pyrroles (**140**); in the general representation in Scheme 31 the intermediate is depicted as a carbanion for simplicity, although *N*-deprotonated species are doubtless involved at some stage, as in Scheme 33.

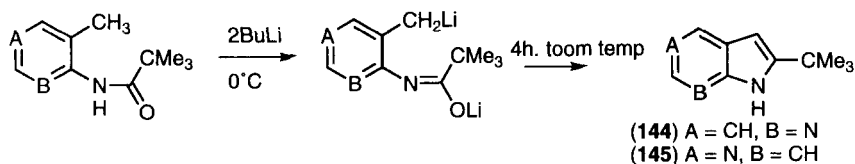
In the earlier work, using bases such as sodium ethoxide, drastic conditions were needed, and the yields were often poor and erratic (68AHC27); examples of the synthesis of pyrrolopyridines (**141**, **142**) and pyrrolo[2,3-*d*]pyrimidines (**143**) by this method are summarized by Scheme 32 (64CPB1024). However, with the use of bases such as butyllithium, much milder conditions can be employed, and good yields obtained even with hindered acyl groups, as in the syntheses of *t*-butylpyrrolopyridines (**144**, **145**) shown in Scheme 33 (83JOC3401).



SCHEME 31



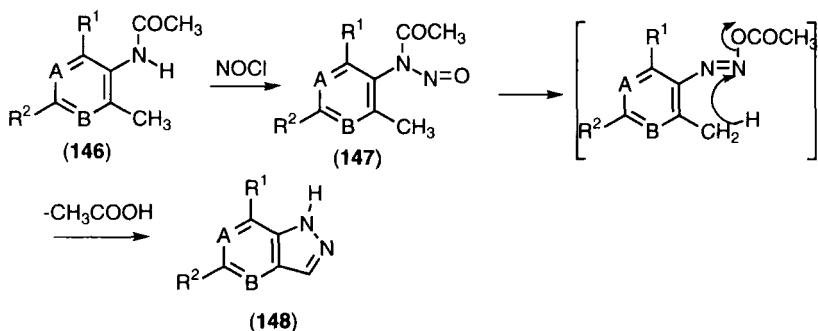
SCHEME 32



SCHEME 33

B. VIA NITROSATION

Acetamidopicolines (**146**) are *N*-nitrosated to give the intermediates (**147**) (HAZARD), which cyclize with elimination of acetic acid on heating in benzene (HAZARD) to give the pyrazolopyridines (**148**) [73JCS(P1)2901; 80JCS(P1)2398]. The proposed mechanism is shown in Scheme 34.



A=CH; B=N; R¹=H; R²=H, Me, OMe, Ph

A=N; B=CH; R¹=Me, OMe, Cl, H, H; R²=H, OMe, Cl

SCHEME 34

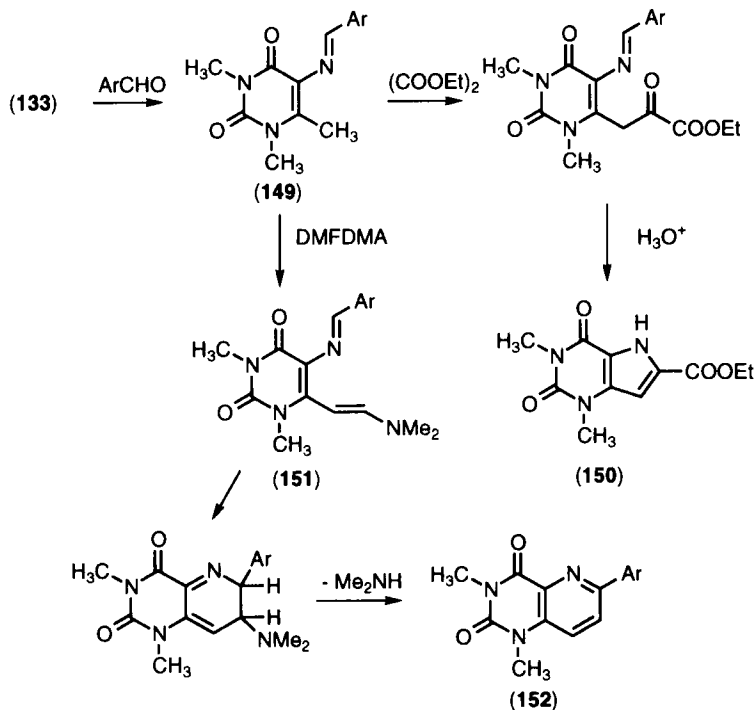
VIII. Methyl and Imino

A one-pot reaction involving an imine intermediate was noted in Section V,D. Related syntheses of pyrrolo[2,3-*d*]pyrimidines (**150**), involving pre-formed anils (**149**) from condensation of the amines (**133**) with aromatic aldehydes, are outlined in Scheme 35 (57CB738).

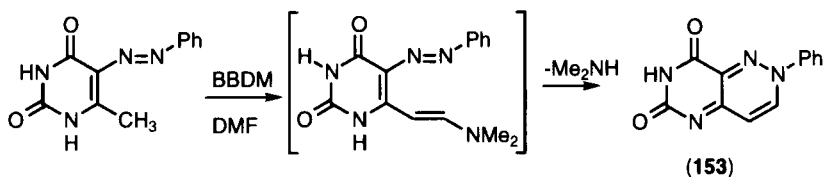
Reaction of the same anils (**149**) with DMFDMA gives pyrido[3,2-*d*]pyrimidines (**152**). As also shown in Scheme 35, the reaction probably involves formation of the enamine (**151**), followed by intramolecular [2 + 4] cycloaddition, followed by elimination of dimethylamine (80S479; 82JHC805).

IX. Methyl and Azo

Reaction of activated methyl groups adjacent to arylazo groups with one-carbon synthons such as BBDM or DMFDMA gives fused pyridazines, by cyclization of the intermediate enamines. An example is the synthesis of



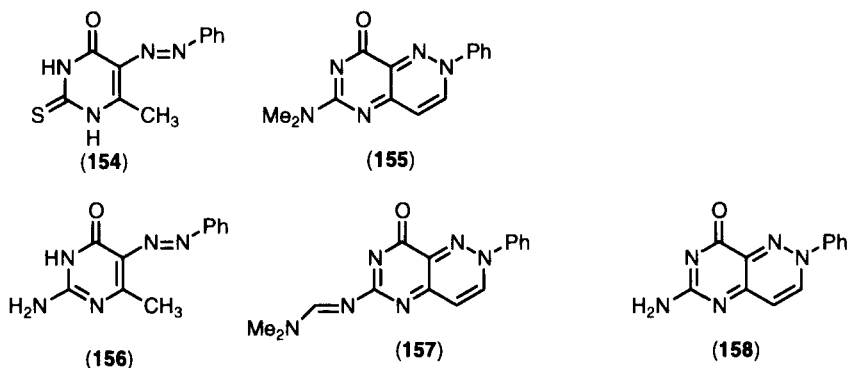
SCHEME 35



SCHEME 36

pyrimido[4,3-*d*]pyridazines (**153**) shown in Scheme 36 (78JOC2536). Variants, showing further reactions of substituents, include the formation of the dimethylamino derivative (**155**) from the thione (**154**) and the amidine (**157**) from the amine (**156**).

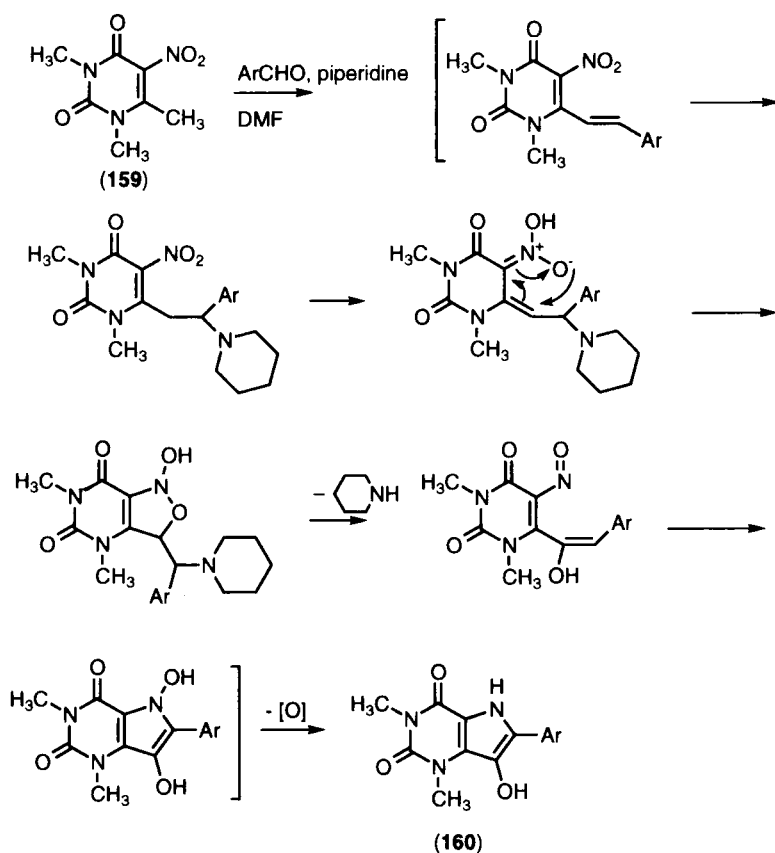
An analogous reaction of the pyrimidinone (**156**) with triethyl orthoformate in trifluoroacetic acid gave the pyrimido[4,3-*d*]pyridazine (**158**) (78JOC2536).



X. Methyl and Nitro

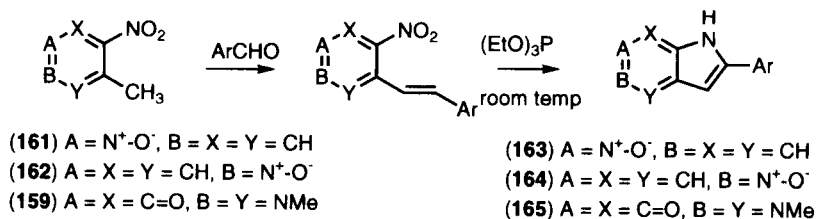
Methylazines are still further activated by the presence of nitro substituents, and there are many heterocyclic syntheses that involve condensation of the methyl group as the first step. Most of them require a subsequent reduction step (cf. Section VI), and not many can be regarded as even potentially one-pot processes. However, the reaction sequence from 1,3,6-trimethyl-5-nitrouracil (**159**) depicted in Scheme 37 provides a genuine one-pot synthesis of pyrrolo[3,2-*d*]pyrimidinediones (**160**). The initial condensation is catalyzed by piperidine, and it is also postulated that piperidine participates in addition-elimination and redox sequences along the lines shown (82CPB3187).

The condensation of nitropicolines (**161**, **162**), and 1,3,6-trimethyl-5-nitrouracil (**159**) with aromatic aldehydes, followed by reduction with tri-



SCHEME 37

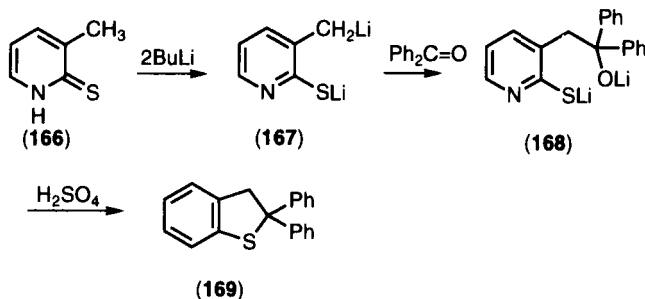
ethyl phosphite under nitrogen, also furnished pyrrolopyridines (**163**, **164**) (65JOC655) and pyrrolo[3,2-*d*]pyrimidines (**165**) (72JMC1168), Scheme 38. In this case the reduction step was carried out separately, but might conceivably be adapted to a "near one-pot" sequence.



SCHEME 38

XI. Methyl and Thiol

The “dianion” (**167**), derived from 3-methylpyridine-2-thione (**166**) by reaction with butyllithium, reacts with benzophenone to yield an intermediate (**168**), which cyclizes on treatment with sulfuric acid to give 2,3-dihydro-2,2-diphenylthieno[2,3-*b*]pyridine (**169**) (68JOC2083), Scheme 39.



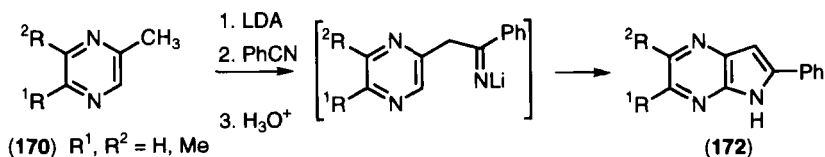
SCHEME 39

XII. Methyl and Ring Carbon

A. REACTIONS VIA α -DEPROTONATION

If a carbanion formed by deprotonation of a methyl group adds to a multiply bonded group, a new nucleophile is formed, which should in principle be capable of cyclization by attack at a ring position. Some preliminary results involving methylpyrazines (**170**) and methylquinoxaline (**171**) and benzonitrile appeared promising, giving pyrrolo[2,3-*b*]pyrazines (**172**) and pyrrolo[2,3-*b*]quinoxaline (**173**) as shown in Scheme 40 (81TL1219), although yields were only modest.

Initial attempts to extend this type of reaction to less activated systems were unpromising, until the requirement for two equivalents of LDA was realized (92T939): it was proposed that a “dianion,” e.g., **174**, was involved. Although details of the reaction pathway remain unclear, this type of reac-

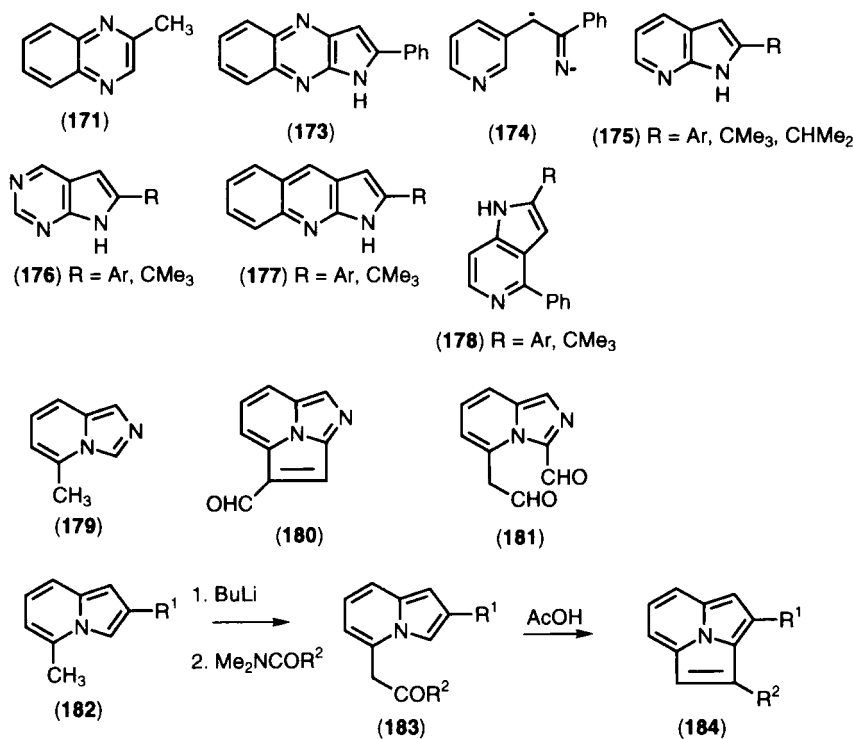


SCHEME 40

tion has been used to prepare, besides the pyrrolo[2,3-*b*]pyrazines (**172**), and pyrrolo[2,3-*b*]quinoxaline (**173**), pyrrolo[2,3-*b*]pyridines (**175**), pyrrolo[2,3-*d*]pyrimidines (**176**), and pyrrolo[2,3-*b*]quinolines (**177**) from the corresponding methyl heterocyclic compounds. When the 2-position of a 3-methylpyridine was blocked, attack at the 4-position led to pyrrolo[2,3-*c*]pyridines such as (**178**).

An analogous pathway could be involved in the formation of 4-formyl-2-azacycl[3.2.2]azine (**180**) in 14% yield by treatment of 5-methylimidazo[1,5-*a*]pyridine (**179**) with butyllithium and DMF, but the route suggested (75JOC1210), via the dialdehyde, (**181**) is also possible.

There is some resemblance to the two-step formation of cycl[3.2.2]azines (**184**) when indolizines (**182**) were treated with butyllithium followed by *N,N*-dimethylamides to give, after hydrolysis, ketones (**183**), which were cyclodehydrated by glacial acetic acid (58JA2020; 59JA1459) as shown in Scheme 41.



SCHEME 41

B. REACTION WITH VILSMEIER REAGENT

Azacycl[3.2.2]azines (**186**) (cf. A, above) can also be prepared by treatment of 6-azaindolizine (**185**) with phosphorus oxychloride in DMF (76JOC351), Scheme 42.

C. REACTION WITH THIONYL CHLORIDE AND SULFURYL CHLORIDE

A complex reaction of 4-methylquinoline (**187**) with thionyl chloride gives a [1,2]dithiolo[3,4-*c*]quinolin-1-one (**189**) [88JCS(P1)3025]; initial formation of the thiocarbonyl chloride (**188**) was proposed, as shown in Scheme 43, and subsequent steps probably involved disulfur dichloride formed *in situ*.

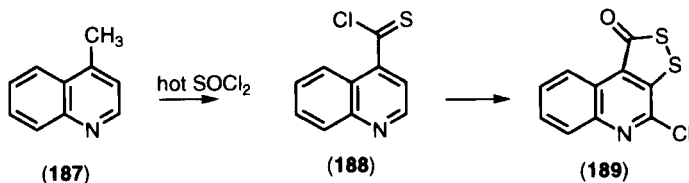
D. BY CYCLOADDITION REACTIONS

1. Dipolar [3 + 2] Cycloaddition

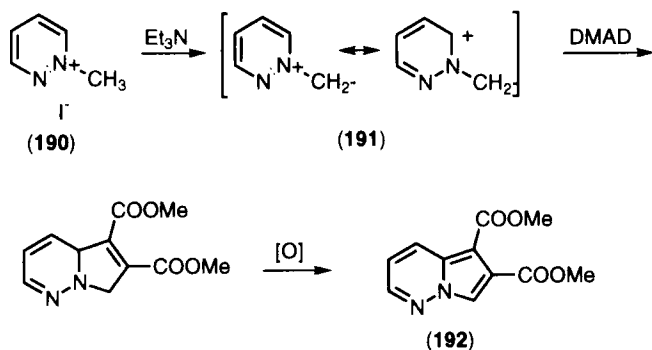
The pyrrolo[1,2-*b*]pyridazine (**192**) can be prepared by treatment of *N*-methylpyridazinium iodide (**190**) with dimethyl acetylenedicarboxylate in the presence of base (73CPB2780). The reaction presumably involves 1,3-dipolar intermediate **191**, as shown in Scheme 44; the final step occurs during workup, but is assisted by chloranil.



SCHEME 42



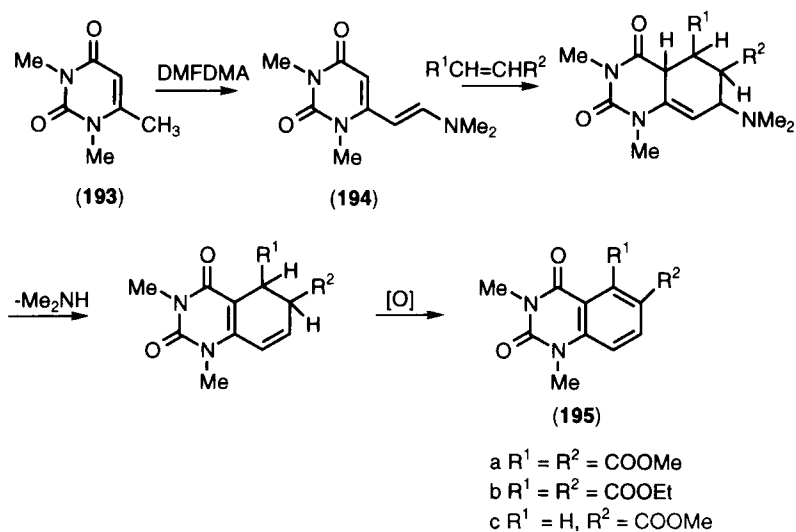
SCHEME 43



SCHEME 44

2. [4 + 2] Cycloaddition

The trimethyluracil (**193**) reacts with DMFDMA to afford the enamine (**194**), which reacts with dienophiles to give 5,6-disubstituted quinazoline-2,4-diones (**195**), via [4 + 2] cycloaddition followed by elimination of dimethylamine, and oxidative aromatization, as shown in Scheme 45 (89CB1673).



SCHEME 45

XIII. Methyl and Ring Nitrogen

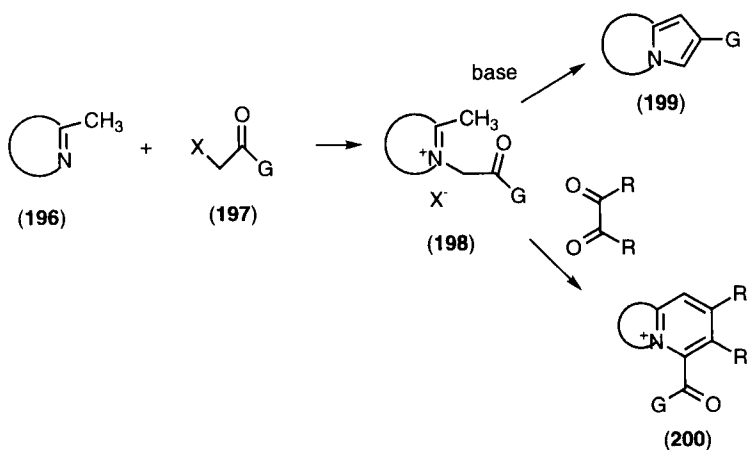
A. REACTION WITH α -HALOGENOCARBONYL COMPOUNDS

Some general reactions of the azinium salts (**198**) produced by reacting α -halogenocarbonyl compounds (**197**) with α -methylazines (**196**) are shown in Scheme 46. They cyclize in the presence of base to give pyrroloazines (**199**) or alternatively condense with α -diketones to give pyridoazinium salts (**200**) (the Westphal synthesis).

Reactions of these types have been extensively utilized for synthesizing a diversity of derivatives of both types of product, and examples to demonstrate their potential are given in the following subsections. Note that the distinction between the reactions covered here and those noted in Section II,D, depending on whether the azinium salt intermediate is, or has to be, isolated, is not always clear-cut.

1. Synthesis of Pyrroloazines

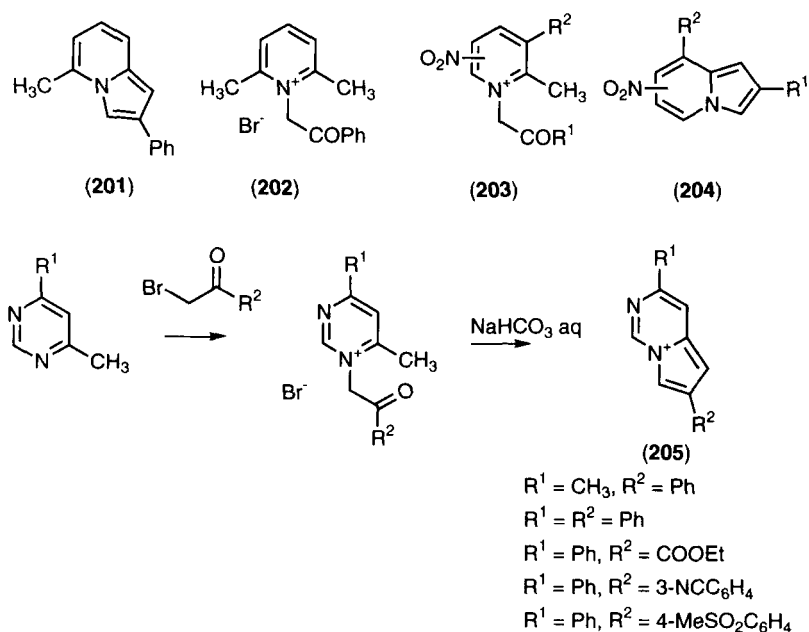
A variety of indolizine derivatives have been prepared by reactions of α -halogenoketones with α -picolines. For example, heating phenacyl bromide with 2,6-dimethylpyridine at 50° for 48 h gives 2-phenyl-5-methylpyrrocoline (**201**), presumably via the intermediacy of the salt (**202**) (27CB1607; 62ZOB2659). Similarly the pyridinium salts (**203**) cyclize in the presence of sodium bicarbonate or triethylamine to give the indolizines (**204**) (76CHE766; 78CHE657).



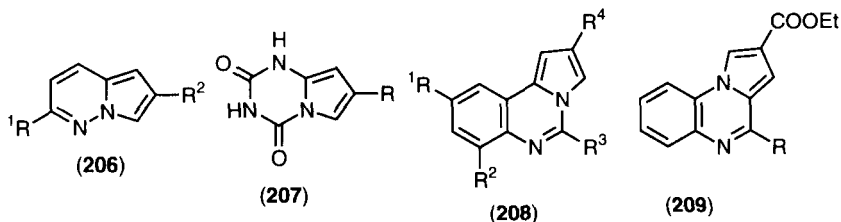
SCHEME 46

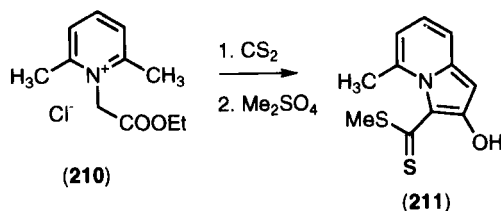
This general approach has been applied to the synthesis of pyrrolo[1,2-*c*]pyrimidines (**205**) (Scheme 47) [56JOC764; 63JOC3212; 68JCS(C)2693], pyrrolo[1,2-*b*]pyridazines (**206**) (71JOC3087), pyrrolo[1,2-*a*]-1,3,5-triazines (**207**) [74JCS(P1)1781], pyrrolo[1,2-*c*]quinazolines (**208**) (79JHC623, 79JHC1497; 81JMC1455), and pyrrolo[1,2-*a*]quinoxalines (**209**) (95JHC1317).

Analogous reactions of α -halogenoesters have been less explored, but an example is shown in Scheme 48. A reaction of 2,6-dimethylpyridine with ethyl chloroacetate gave the pyridinium salt (**210**), which on reaction with carbon disulfide in the presence of sodium hydroxide and subsequent methylation with dimethyl sulfate gave methyl 5-methyl-2-hydroxyindolizine-3-dithiocarboxylate (**211**) (81YZ980).



SCHEME 47



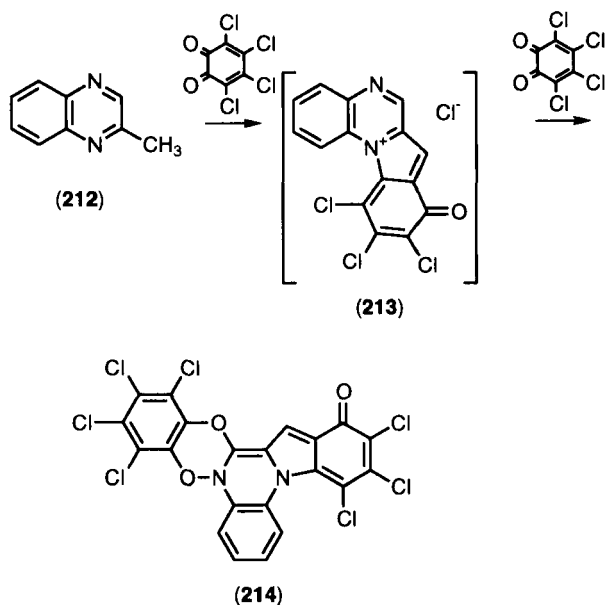


SCHEME 48

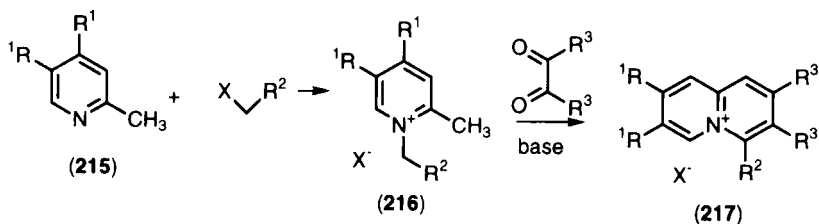
An interesting special case is the reaction of 2-methylquinoxaline (**212**) with tetrachloro-*o*-benzoquinone (Scheme 49), which gives the hexacyclic product (**214**), presumably via the intermediate salt (**213**) (70CJC327).

2. Synthesis of Pyridoazinium Salts

The picolinium salts (**216**) obtained by reactions of the picolines (**215**) with α -halogenoketones, and also with α -halogenoesters and α -halogenonitriles (and even those from benzyl halides), react with α -dicarbonyl compounds in the presence of base to give quinolizinium salts (**217**) as shown in Scheme 50; salts derived from 1-methylisoquinoline similarly gave



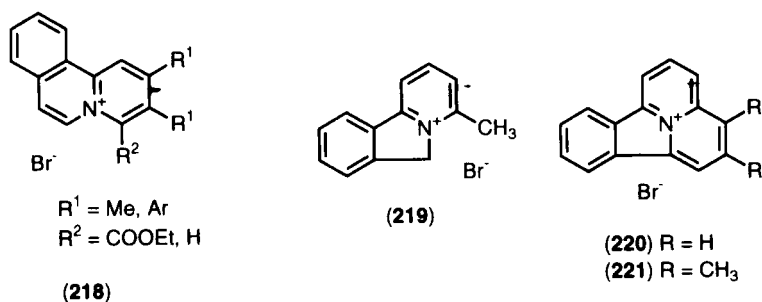
SCHEME 49



SCHEME 50

benzo[*d*]quinolizinium salts (**218**), in some cases with loss of an ethoxycarbonyl group by hydrolysis and decarboxylation (85JHC681; 86JHC1151).

The Westphal condensation between the azoniafluorene salt (**219**) and glyoxal (in its masked form as 2,3-dihydroxy-1,4-dioxane) or dimethylglyoxal in the presence of triethylamine gave the 10*c*-azoniafluoranthene salts (**220**, **221**), respectively (89AGE588; 91JOC4858).

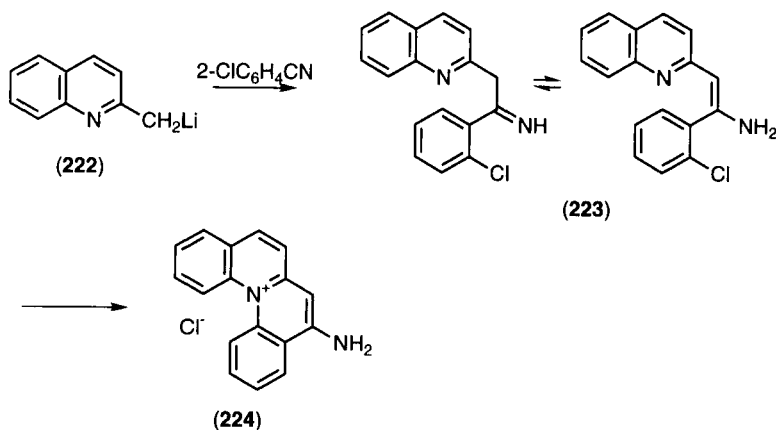


B. REACTION WITH *o*-CHLORONITRILES AND *o*-CHLOROCARBONYL COMPOUNDS

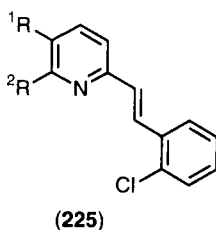
The enamine (**223**) obtained by reacting 2-chlorobenzonitrile with 2-lithiomethylquinoline (**222**) is converted into the dibenzo[*c,f*]quinolizinium chloride (**224**) on heating at 235° (79JHC753), Scheme 51. This two-step process, and related photocyclizations of the azastilbenes (**225**) obtained by condensation of the appropriate α -methylazines with *o*-chlorobenzaldehyde (66JOC3683; 70JHC1421; 91CL1355), could have some potential for development as one-pot procedures.

C. REACTION WITH ETHOXYMETHYLENEACETOACETATES

Condensation of 1-methyl-3,4-dihydro- β -carboline (**226**) with ethyl ethoxymethyleneacetoacetate in dry methanol at room temperature for



SCHEME 51



24 h gave 3-acetyl-4-oxo-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizine (**227**) as shown in Scheme 52 (84H233).

D. REACTION WITH DIARYL MALONATES

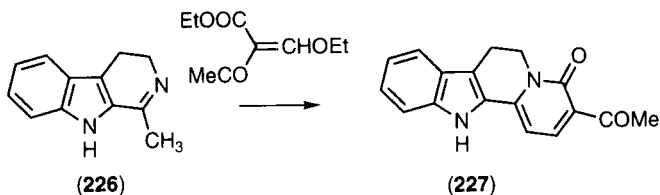
The reaction of monosubstituted bis(2,4,6-trichlorophenyl)malonates (**229**) with 3-aryl-2-methyl-4-quinazolones (**228**) at fusion temperatures gives 2,5-disubstituted 5,6-dihydro-1*H*-pyrido[1,2-*a*]quinazoline-1,6-diones (**230**) in 30–50% yields, as shown in Scheme 53 [81ZN(B)252].

E. REACTION WITH DIMETHYL ACETYLENEDICARBOXYLATE

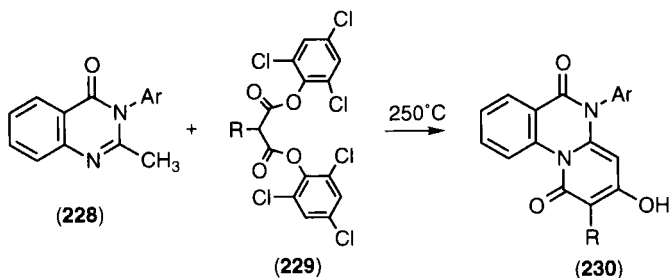
A quite general type of reaction is typified by those of 2-methylquinoline (**231**) [68JCS(C)926] and 2-methylquinoxaline (**232**) [66JCS(C)2218; 68-JCS(C)378] with two equivalents of dimethyl acetylenedicarboxylate to

give mixtures of isomeric dihydroazepinoquinolines (**233**, **234**) or dihydroazepinoquinoxalines (**235**, **236**).

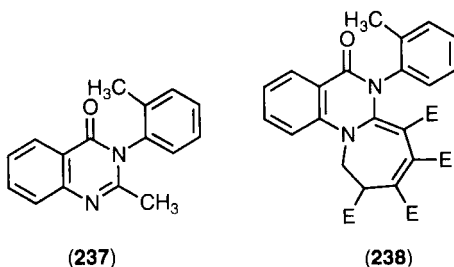
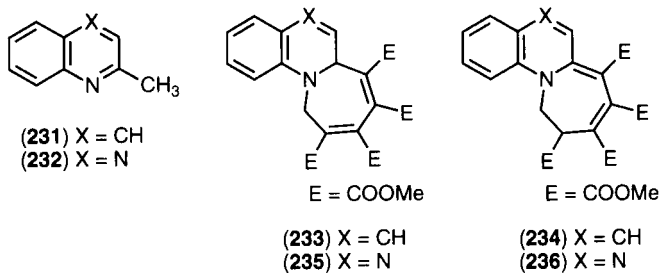
Similarly, the azepino[1,2-*a*]quinazoline (**238**) was synthesized by the reaction of dimethyl acetylenedicarboxylate with the 2-methylquinazolin-4-one (**237**) (72JHC1227).



SCHEME 52

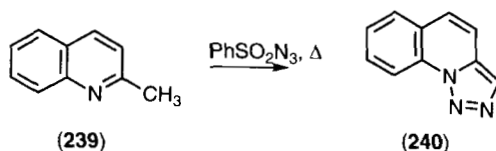


SCHEME 53

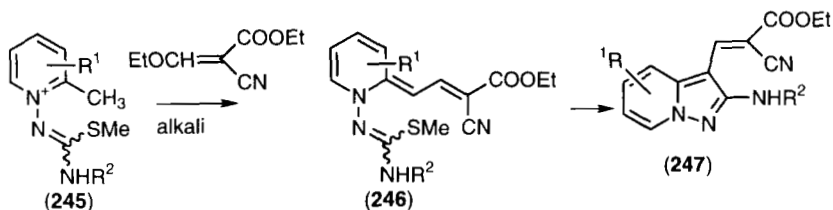
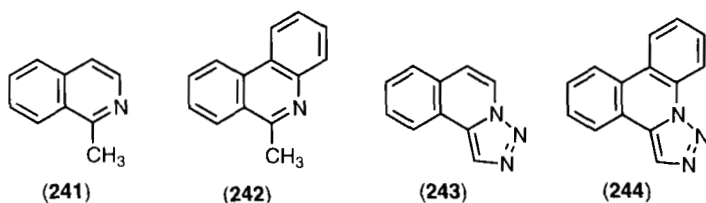


F. REACTION WITH BENZENESULFONYL AZIDE

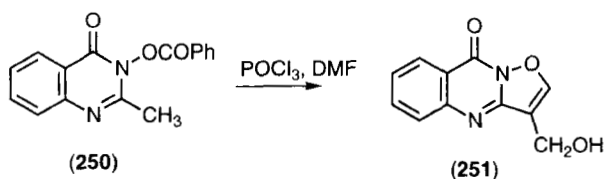
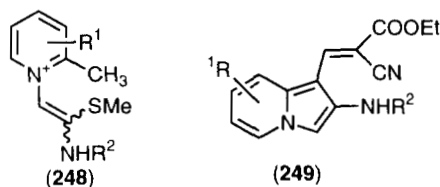
When 2-methylquinoline (**239**) is heated with benzenesulfonyl azide, 1,2,3-triazolo[1,5-*a*]quinoline (**240**) is obtained, Scheme 54 (72JOC2022). Similarly, 1-methylisoquinoline (**241**) and 6-methylphenanthridine (**242**) give the corresponding triazoles (**243**, **244**).



SCHEME 54



SCHEME 55



SCHEME 56

XIV. Miscellaneous

Reactions of the pyridinium salts (**245**) with ethyl ethoxymethylenecyanoacetate give the pyrazolo[1,5-*a*]pyridine (**247**) via the intermediate (**246**), Scheme 55, and analogous reactions of the pyridinium salts (**248**) give the indolizines (**249**) [80JCR(M)0404, 80JCR(S)18].

On reaction with Vilsmeier reagent, the quinazolinone (**250**) gave the isoxazolo[3,2-*b*]quinazolinone (**251**), Scheme 56 [86IJC(B)709].

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71JOC3087
72CB2344
72JHC843
72JHC1227
72JMC1168
72JOC2022
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The Chemistry of C-Nucleosides and Their Analogs I: C-Nucleosides of Hetero Monocyclic Bases

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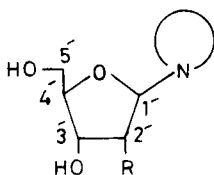
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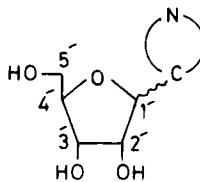
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I. Introduction

Normal or *N*-nucleosides (**1**), the building units of DNA or RNA, have Cl' of their sugar subunits (2-deoxy-D-ribose or D-ribose) linked to heterocycle subunits (purine or pyrimidine bases) through carbon–nitrogen bonds.



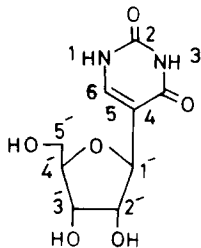
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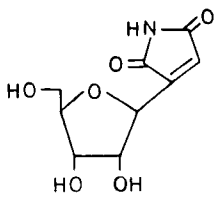
2

R = H or OH

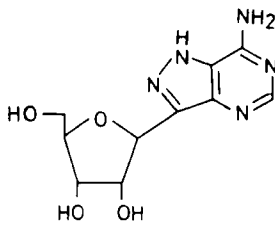
Naturally occurring *C*-nucleosides (**2**), in contrast, have C1' of their sugar moieties linked to various types of nitrogen-containing heterocycles through a carbon-carbon bond. *C*-Nucleosides were not known before 1957, when pseudouridine [5-(β -D-ribofuranosyl)uracil] (**3**), the first member of this class of compounds, was isolated (57JBC907; 65MI3; 66MI1; 70MI5) from yeast RNA, and the elucidation of its structure was accomplished 2 years later [59BBA(32)569; 60JBC1488]. Since then other members of this important class of compounds have been successively isolated, namely, showdomycin [2-(β -D-ribofuranosyl)maleimide] (**4**) [64JAN(A)148], formycin {7-amino-3-(β -D-ribofuranosyl)pyrazolo[4,3-*b*]pyrimidine} (**5**) [64JAN(A)96], formycin B (less commonly named laurusin) {3-(β -D-ribofuranosyl)-pyrazolo[4,3-*b*]pyrimidine-7-one} (**6**) [65ABC375, 65JAN(A)175], pyrazofurin (formerly named pyrazomycin) [5-carboxy-amido-4-hydroxy-3-(β -D-ribofuranosyl)pyrazole] (**7**) (69MI2, 69MI4; 71PAC489), pyrazofurinB [5-carboxamido-4-hydroxy-3-(α -D-ribofuranosyl)pyrazole] (**8**) (69MI1; 71MI11), oxazinomycin (less commonly called minimycin) [5-(β -D-ribofuranosyl)-1,3-oxazine-2,5-dione] (**9**) [71GEP2043946, 71JAN797; 72JAN44, 72JAN151], and ezomycins (**10**). 1-Methylpseudouridine (**11**) (76JAN818) and 3-methylpseudouridine (**12**) (89JAN1248) were isolated from the fermentation broths of *Streptomyces platensis* and *Nocardia lactamdurans*, respectively. Very recently, 7-amino-3- β -D-ribofuranosylpyrrolo[3,2-*d*]pyrimidine (**13**)



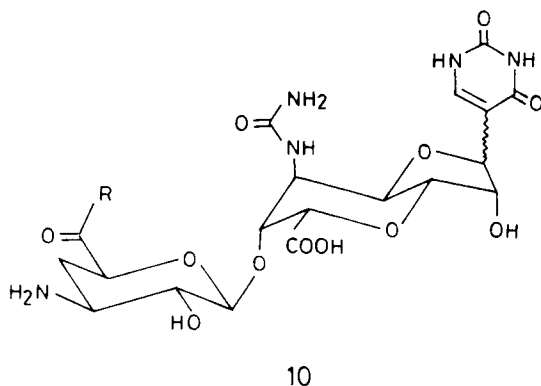
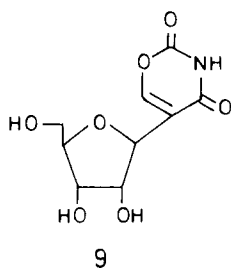
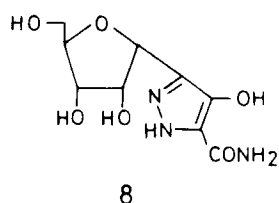
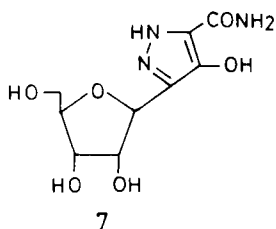
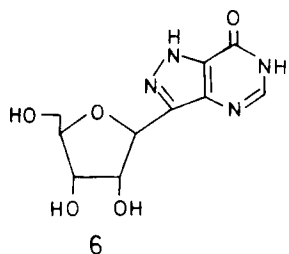
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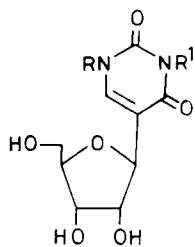


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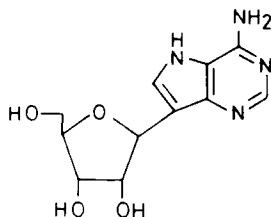


and its 5'- α -D-glucopyranosyl derivative (**14**) were isolated from the cyanobacterium *Anabaena affinis* strain VS-1 (blue-green alga), and their structures were elucidated (93JA2504). The C-nucleoside antibiotic CV-1 (**15**) seems to be the only acyclo C-nucleoside of natural origin. CV-1 was isolated from a strain of *Streptomyces* sp. II, and its 5-hydroxy-4-(*p*-arabino-tetritol-1-yl)imidazolidine-2,5-dione structure (**15**) was determined (87-JAN727).

C-Nucleosides exhibit important biological activities as a result of isosterically mimicking N-nucleoside metabolites. The former replace the latter in

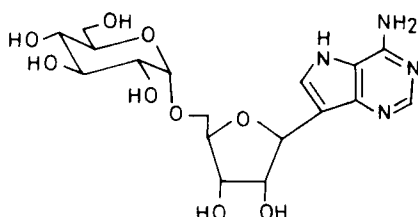


11, R = Me, R¹ = H



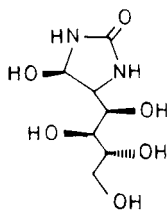
12, R = H, R¹ = Me

13

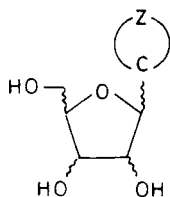


vital reactions, without being able to undergo the natural metabolic fate because, in contrast to the C–N glycosidic linkage in *N*-nucleosides, the C-glycosidic linkage of *C*-nucleosides resists enzymatic hydrolysis (68MI3; 75MI2; 81MI1). The naturally occurring *C*-nucleosides **4–10** possess antibacterial, antiviral, and antitumor activities (70MI5; 76MI1, 76MI2; 78MI1; 79MI4, 79MI6; 82MI4; 83MI2) as a result of interfering with key biological processes such as biomethylation, nucleic acid metabolism, and protein or chitin biosynthesis (76MI6).

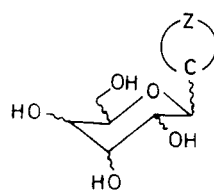
In literature, the term “*C*-nucleosides” is sometimes bestowed on saccharide derivatives of heterocycles not containing nitrogen. However, since all of the heterocyclic subunits of naturally occurring nucleosides are nitrogen-containing, these derivatives are much more appropriately categorized as *C*-glycosides (**16, 17**) (63MI2; 65MI2; 92T8545).



15

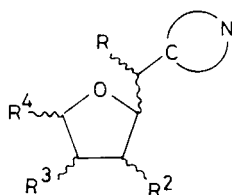


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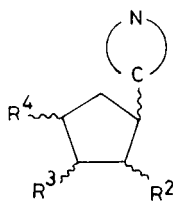


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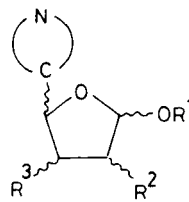
Z = C, O, S



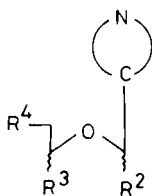
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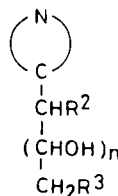
19



20



21



22

R = H or OH; R¹ = H or alkyl; R², R³ = H or OH; R⁴ = H or (CHOH)_n

In this review, *C*-nucleosides are meant to be *C*-linked saccharide derivatives of nitrogen-containing heterocycles. In the present part of this review, the different types of *C*-nucleosides of hetero monocyclic bases are systematically classified according to the size and complexity of the nitrogen heterocycle, starting with those having one nitrogen atom in a three-membered ring and proceeding to more complex heterocycles. Nucleosides of heterocycles containing, in addition to nitrogen, other heteroatoms are arranged in the order oxygen, sulfur, and selenium. Within a particular class, *C*-nucleosides are discussed first followed by their analogs in the sequence homo (**18**), carbocyclic (**19**), reverse (**20**), and acyclic *C*-nucleosides (**21** and **22**). The literature has been surveyed up to issue number 13, Volume 123, 1995, of the *Chemical Abstracts*.

II. Definitions of Analogs

A. HOMOCYCLIC *C*-NUCLEOSIDES

These are *C*-nucleoside analogs (**18**) in which the cyclic sugar moiety and the heterocyclic base are flanked by one carbon.

B. CARBOCYCLIC *C*-NUCLEOSIDES

In this type of *C*-nucleoside analog (**19**), a hydroxylated cyclopentyl residue replaces the ribofuranosyl moiety.

C. REVERSE *C*-NUCLEOSIDES

Inverse (72HCA2816), reverse (73HCA1303), or pseudo (75MI1; 89MI8) are terms used to describe *C*-nucleoside analogs (**20**) having their C–C linkage between C-4' or C-5' of a furanose, or C-6' of a pyranose sugar moiety and the heterocyclic base, rather than having a C–C glycosidic linkage (**20**). However, to avoid confusion with “pseudo” prefixed names such as pseudouridine (**3**) or pseudocytidine, which have traditionally been used to distinguish these *C*-nucleosides from their *N*-linked analogs (uridine and cytidine), the term reverse *C*-nucleosides is preferentially used throughout this review.

D. ACYCLO *C*-NUCLEOSIDES

Acyclo *C*-nucleosides have their nitrogen heterocycles C–C linked to a polyhydroxyalkyl ether (truncated sugar residue) (**21**) or polyhydroxyalkyl

chain (alditolyl residue) (**22**). Acyclo *C*-nucleosides of synthetic origin have long been known (70MI1) prior to the isolation of the naturally occurring *C*-nucleosides. After characterization of these compounds and the advent of the potent antiviral *N*-nucleoside "acyclovir" [9-(2-hydroxyethoxymethyl)guanine] (78NAT583), the synthesis and investigation of biological activities of acyclo *C*-nucleosides have gained much importance (86JHC289). Carbon-carbon linked polyhydroxyalkyl heterocycles (**22**) are valuable precursors for the synthesis of *C*-nucleosides (**2**) through the acid-catalyzed cyclodehydration of their polyhydroxyalkyl chains [51MI1; 56MI1; 65MI2; 72MI5; 80JCS(P1)2561].

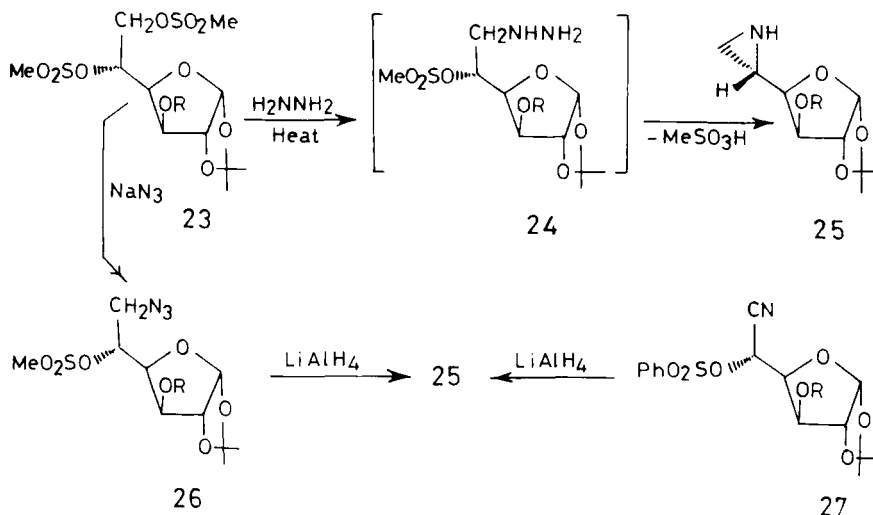
III. General Methods of Synthesis

Because of the numerous biological activities associated with the structures of the naturally occurring *C*-nucleosides (70MI5; 78MI1; 79MI5; 79MI6; 80MI3; 81MI1; 85MI14), extensive work has been targeted toward their synthesis as well as that of their analogs (76MI1, 76MI2; 80YKG756, 80YKG862, 80YKG997; 83MI4; 85MI9, 85MI10; 86JHC289; 87YKG212; 89YKG707; 92MI9; 94MI2). The synthesis of analogs carrying various nitrogen heterocycles is rationalized in terms of achieving more potent and more specific biological activities. Four approaches are used in the synthesis of *C*-nucleosides: (1) ionic, free-radical, or heavy metal-mediated C—C bond formation between a suitably protected sugar derivative and the preformed heterocycle, (2) stepwise construction of the heterocycle subunit onto a properly functionalized *C*-glycosyl subunit (76JOC84), (3) chemical transformation of an easily accessible *C*-nucleoside to a less accessible one [71JCS(C)2443], and (4) total synthesis from noncarbohydrate starting materials (73TL1525; 75TL985). The last approach is less frequently used in view of the many steps it requires to create the chiral centers of the sugar residue as well as stereochemical control of its β -anomer.

IV. Azirine *C*-Nucleosides

A. AZIRINE REVERSE *C*-NUCLEOSIDES

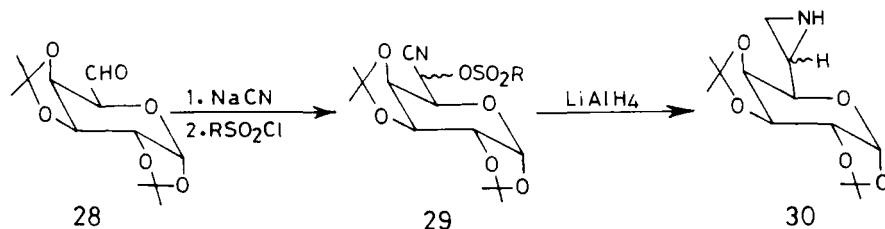
These compounds were prepared to study their properties as alkylating agents in cancer chemotherapy. In an approach toward their synthesis, the two adjacent sulfonate groups of **23** were consecutively displaced by a single hydrazine molecule; configurational inversion took place at C5' to give the azirine reverse *C*-nucleoside **25** (68AGE134; 69CB820) (Scheme 1).



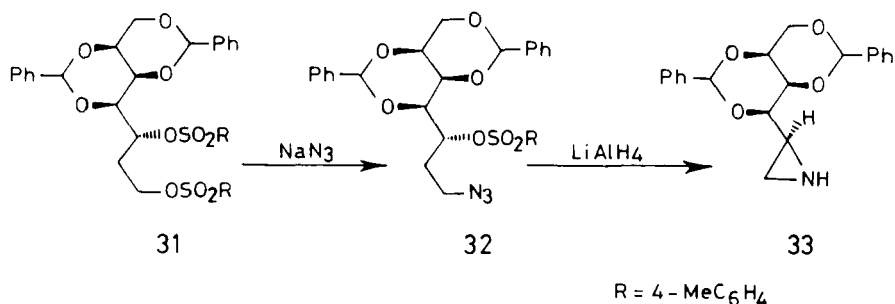
SCHEME 1

Reduction of 6-azido-6-deoxy-5-*O*-sulfonylfuranose derivatives such as **26** (68CPB188, 68CPB962, 68CPB2471, 68CPB2477; 69CPB1664; 75BCJ610) or 5-*O*-sulfonyluronic acid nitriles such as **27** (70BCJ2501) also gave **25** (Scheme 1). A mixture of the two stereoisomers of the pentopyranose reverse *C*-nucleosides **30** were similarly prepared by reduction of the two C6 epimeric hepturonic acid nitrile 5-sulfonates **28** (69CPB1974) (Scheme 2).

The azirine nucleus of these compounds undergoes facile ring opening in order to dispose of angle strain (77USP4031304). Compounds of this class showed no activity against leukemia L-1210 cells (68CPB2471; 69CPB1664).



SCHEME 2



SCHEME 3

B. AZIRINE ACYCLO C-NUCLEOSIDES

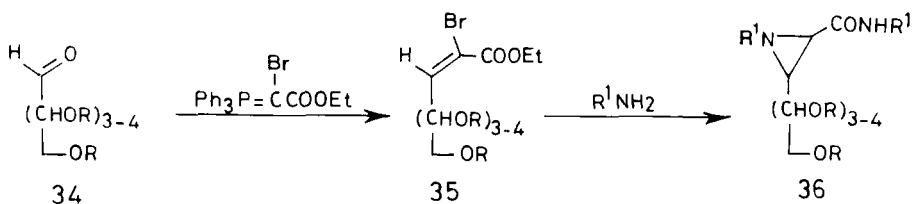
Reduction of the 6-azido-6-deoxy-5-O-(4-tolylsulfonyl)-D-glucitol derivative **32** gave the azirine acyclo C-nucleoside **33** (70MI10, 70MI11) (Scheme 3).

The 1,2-disubstituted azirine acyclo C-nucleosides **36** were synthesized by cyclization of the α -bromo- α,β -unsaturated esters **35** with primary amines (67IZV2691) (Scheme 4).

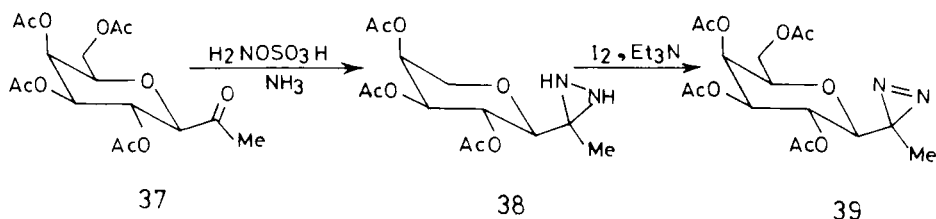
V. Diazirine C-Nucleosides

A. DIAZIRINE C-NUCLEOSIDES

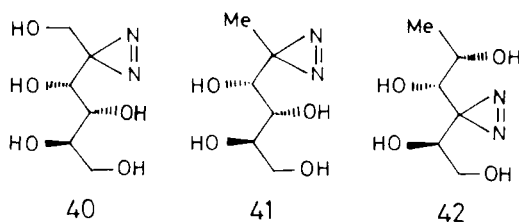
The first compound of this class (**39**) was synthesized to test its applicability in photoaffinity labeling of sugar-binding proteins. Cyclocondensation of the α -D-galactopyranosylmethyl ketone (**37**) with ammonia and hydroxylamine O-sulfonic acid followed by oxidation with iodine in the presence of triethylamine gave **39** (85MI3) (Scheme 5).



SCHEME 4



SCHEME 5



B. DIAZIRINE ACYCLO C-NUCLEOSIDES

To study the relation between structure and photoaffinity labeling of sugar-binding proteins, a number of diazirine acyclo C-nucleosides (**40–42**) have been synthesized using a similar sequence to that shown in Scheme 5 (93MI5).

VI. Azole C-Nucleosides

Azole C-nucleosides are among the most extensively studied C-nucleosides because of the many attempts directed toward the synthesis of showdomycin (**4**), the naturally occurring azole C-nucleoside antibiotic, as well as the synthesis of its analogs. Long before recognition of C-nucleosides, however, polyhydroxyalkyl pyrrole compounds (pyrrole acyclo C-nucleosides) were synthesized to study the reaction of amino sugars with 1,3-dicarbonyl compounds.

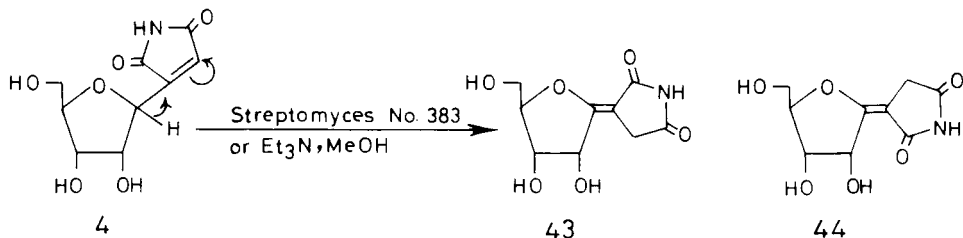
A. THE NATURALLY OCCURRING AZOLE C-NUCLEOSIDE ANTIBIOTIC "SHOWDOMYCIN" AND ITS CONGENERS

Showdomycin (**4**) was first isolated in 1964 by Nishimura [64JAN(A)148] from culture filtrates of *Streptomyces showdoensis* and then from other

strains of the same microorganism (65FRPCAM91; 68MI1, 68MI2). The 3-(β -D-ribofuranosyl)-3-pyrroline-2,5-dione [2-(β -D-ribofuranosyl)maleimide] structure **4** of showdomycin was independently elucidated by American (67PNA548) and Japanese (67TL4105) investigators on the basis of UV, IR, and ^1H NMR spectral measurements as well as hydrazinolysis, stoichiometric hydrogenation, and periodate oxidation. Three-dimensional X-ray diffraction [67JCS(CC)975; 69JCS(B)843; 70JCS(B)1709], ^{13}C NMR (73JHC427), and mass spectral (68JHC459) analyses also confirmed the assigned structure. The mass spectrum of showdomycin, as well as those of the other C-nucleosides, is characterized by a peak at m/z B+30 corresponding to the mass of the heterocyclic base B carrying a C-linked protonated formyl group (B-CHOH). This diagnostic peak contrasted the B+1 and/or B+2 peak(s) characterizing N-nucleosides. X-ray analysis of showdomycin established the syn conformation relation between the azole and the sugar moieties [70JCS(B)1709]. Studies on the biosynthesis of showdomycin indicated that its maleimide ring is derived from glutamate residues (72B2578).

Showdomycin exhibited broad-spectrum antibiotic activity against both gram-positive and gram-negative bacteria and showed particularly extreme activity against *Streptococcus hemolyticus* and *Streptococcus pyrogenes* [64FRPm2751, 64JAN(A)234]. At concentrations not affecting bacterial growth, showdomycin evoked marked biosynthesis of labeled RNA in *Escherichia coli*, *Bacillus cereus*, and *Alcaligenes faecalis* that is no longer complementary to DNA (70MI2). It inhibits the incorporation of amino acids, purine, and pyrimidine bases into macromolecules [68ABC1021, 68JAN(A)250; 69BBA(192)367], inhibits DNA-dependent RNA polymerase (70MI4, 70MI6), and strongly inhibits deoxycytidine uptake through membrane vesicles of *E. coli* [73BBA(311)496]. In addition to its antibiotic activity, showdomycin revealed marked antitumor activity against Ehrlich ascites cells in mice [64FRPm2751, 64JAN(A)234], low activity against ascites hepatoma AH-130 in rats [64JAN(A)234], increase of vascular permeability in rats [67JAN(A)369], strong inhibition of bovine liver UDP- α -glucose dehydrogenase (68MI4), and slight inhibition of bovine mammary UDP-galactose-4-epimerase (70MI3). The biological activities of showdomycin were attributed to its ability to alkylate thiol groups in enzymes through addition to the maleimide double bond (68MI4; 72BBR(49)1007]. This rationale was confirmed by finding out that (i) the activities are reversed by thiols such as 2-mercaptoethanol (68MI4) and (ii) the toxicity of alkylating agents is considerably enhanced in the presence of showdomycin (69JAN43).

When introduced into cultures of *Streptomyces* NO. 383 or when treated with triethylamine, showdomycin (**4**) underwent a double bond shift to give



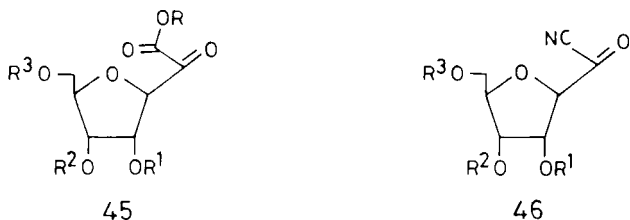
SCHEME 6

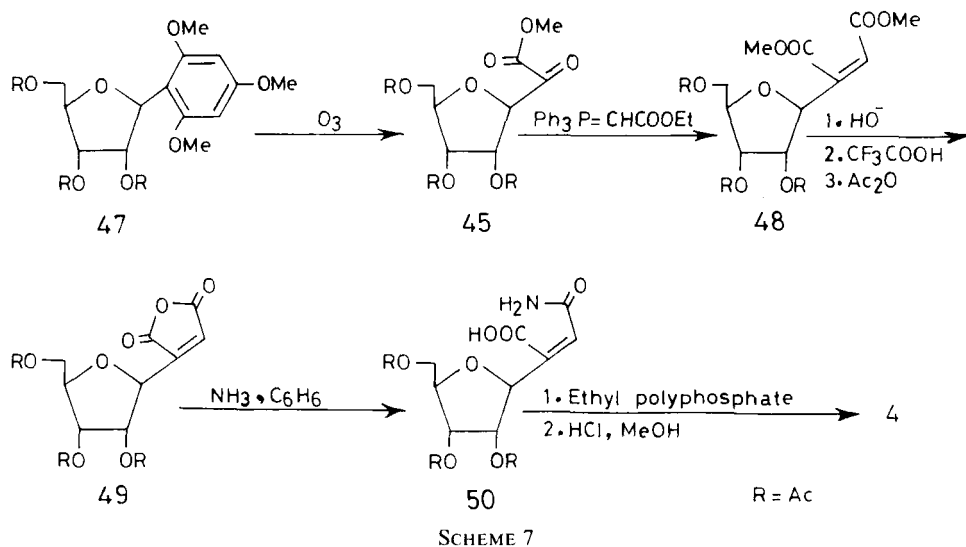
isoshowdomycin (**43** or **44**), which lacked the antibiotic activities of the parent compound (72ABC451) (Scheme 6).

Probably because of the various biological activities of showdomycin, its synthesis has been the subject of a large number of publications that involved all of the general methods for the synthesis of C-nucleosides (Section III) (76MI1, 76MI2; 82MI4; 83MI2; 85MI9). Most of the reported syntheses involved stepwise elaboration of the maleimide subunit and relied mainly on the protected β -glycosyl α -keto ester **45** and, to a lesser extent, β -glycosyl α -keto nitrile **46** as starting materials.

The first synthesis of showdomycin (**4**) was that reported in 1970 by Kalvoda, Farkas, and Šorm in which a Wittig reaction of ethoxycarbonylmethylene triphenylphosphorane and the β -D-ribofuranosyl α -keto ester **45** gave the β -D-ribofuranosylmaleic ester **48**. Hydrolysis of **48**, anhydride formation followed by cycloamination, and removal of the protective groups gave showdomycin (**4**) (70TL2297) (Scheme 7). The tri-*O*-benzyl- β -D-ribofuranosyl α -keto ester **48** was prepared by catalytic dimethoxycarbonylation of tri-*O*-benzyl- β -D-ribofuranosylacetylene (**52**) and then transformed to showdomycin (**4**) [79JCS(P1)225] (Scheme 8). α -Showdomycin was similarly prepared from the α -analog of **52** and found to be inactive against bacteria, fungi, yeast, viruses, and protozoa [81JCS(P1)2267]. This indicated that the antibiotic activity of showdomycin is associated with the β -anomeric configuration of the sugar moiety.

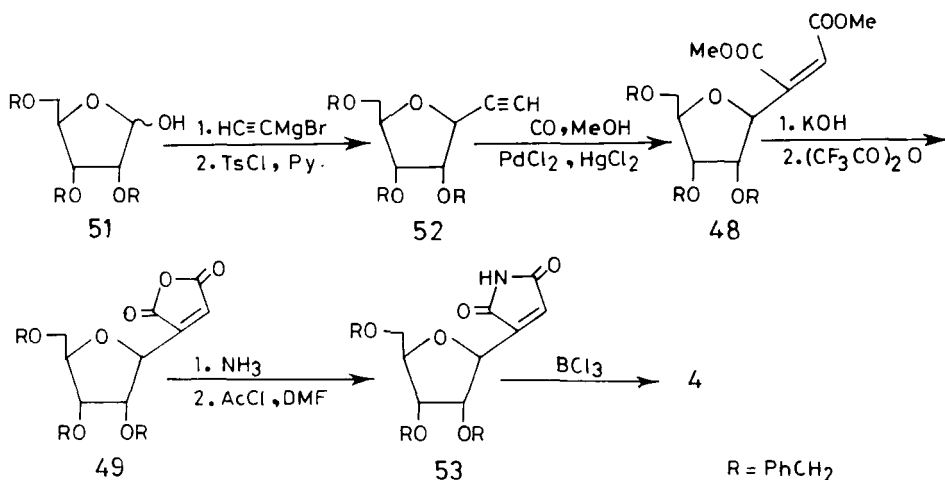
Trummlitz and Moffatt prepared the tri-*O*-benzyl- β -D-ribofuranosylglyoxylic ester **45** from the 2,5-anhydro-D-allose derivative **54** and cyclized it



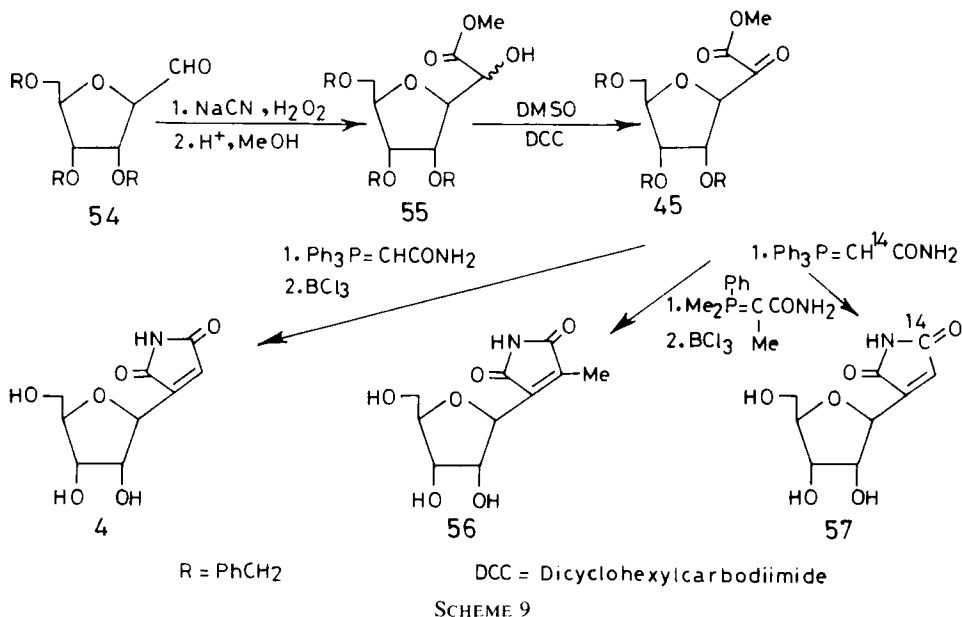


SCHEME 7

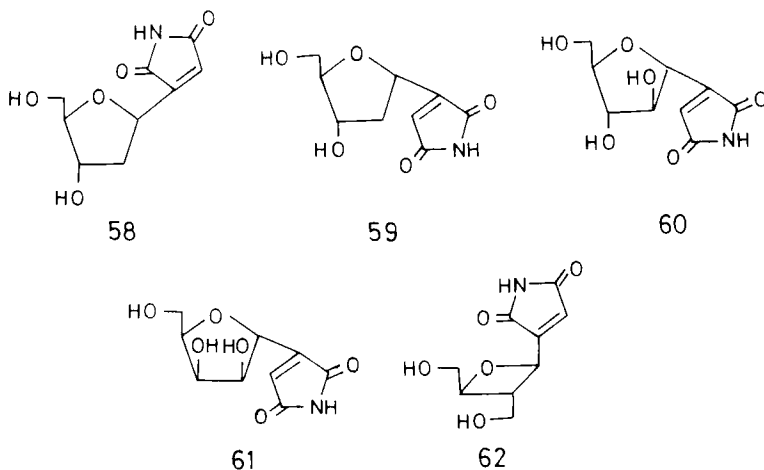
in one step with carboxamidomethylene triphenylphosphorane to give, after de-*O*-benzylation with boron trichloride, showdomycin (**4**) (73JOC1841). Cyclization of **45** with the appropriate Wittig reagent gave 2-methylshowdomycin (**56**) (75JOC3352) and $^{14}C_5$ labeled showdomycin (**57**) (78MI2) (Scheme 9). An analog of **45** carrying the acid-sensitive 2,3-*O*-isopropyl-

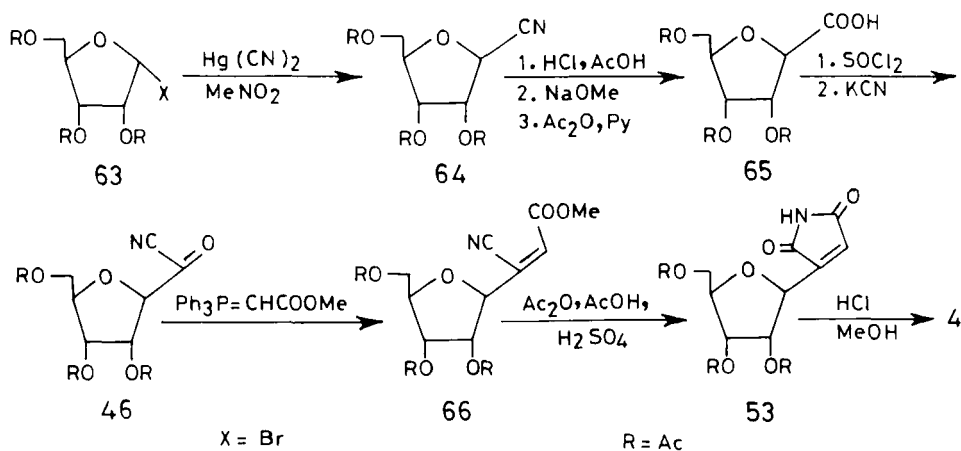


SCHEME 8



dene-5-*O*-trialkylsilyl protective groups was similarly cyclized in a single step to the corresponding *O*-protected showdomycin (**85JA4289**). 2'-Deoxyshowdomycin (**58**) [81TL683; 90JCS(CC)84] and 2'-deoxy- α -showdomycin (**59**) (88TL1841), as well as the α -D-arabinofuranosyl **60** (88TL1841, 88TL2711), the α -D-lyxofuranosyl **61** (88TL2711), and the tetraoxetanose



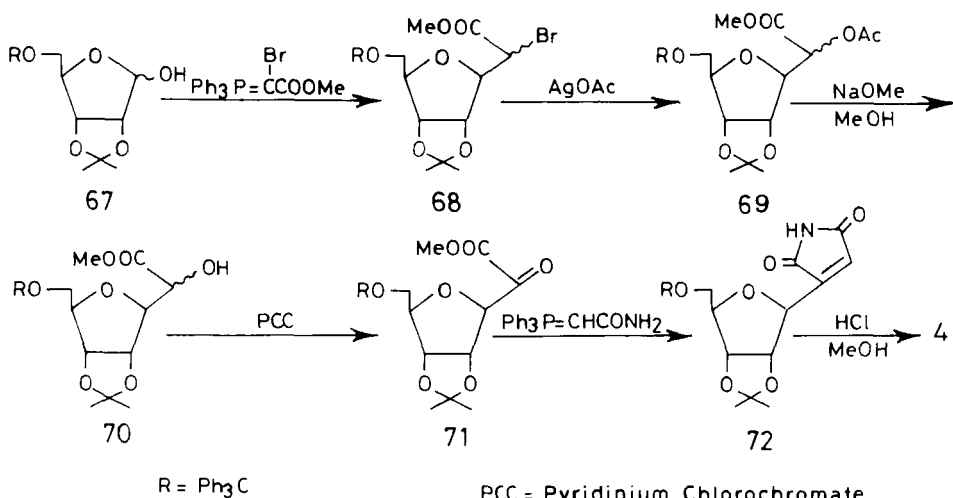


SCHEME 10

62 (91TL2399) analogs of showdomycin, were prepared from the corresponding derivatives of **54**.

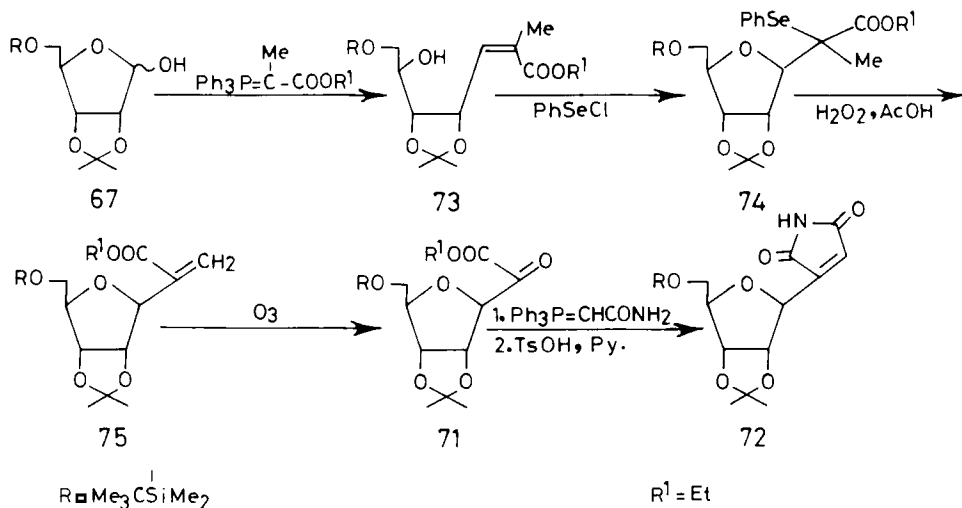
In 1976, Kalvoda reported his second synthesis of showdomycin (**4**) from the 2,5-anhydro-D-allonitrile **64** by stepwise construction of the maleimide residue as shown in Scheme 10 (76MI14).

Elaboration of the four carbons of the maleimide moiety onto the C1 unprotected D-ribofuranose derivative **67** was made by doubly applying a Wittig reaction as shown in Scheme 11 (84H2195, 84MI2; 88T3715).



PCC = Pyridinium Chlorochromate

SCHEME 11

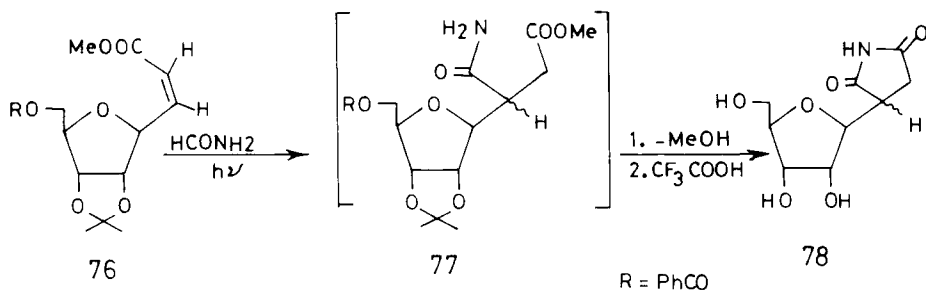


SCHEME 12

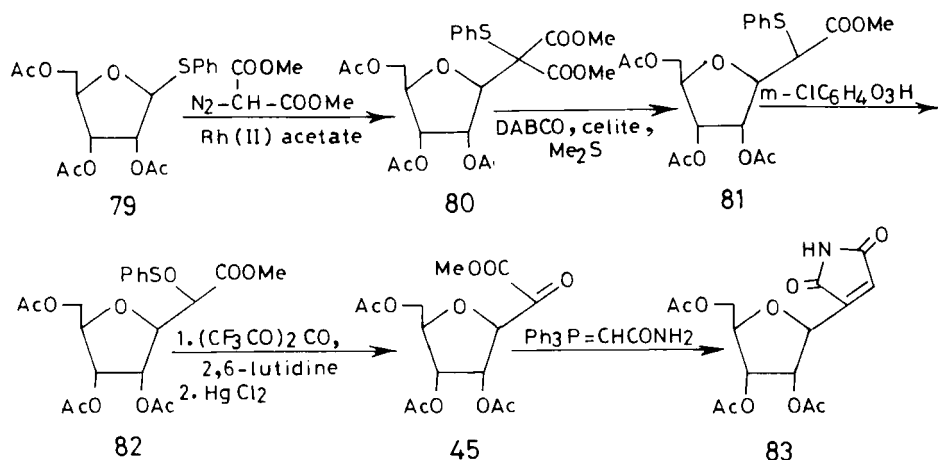
Selenophenylation of the acyclo unsaturated ester **73** followed by deselenophenylation of **74** gave the 2-(β -D-ribofuranosyl)acrylic ester **75**. Ozonolysis of **75** and cyclization of **71** with carboxamidomethylene triphenylphosphorane gave the *O*-protected showdomycin **72** [84JCS(P1)657] (Scheme 12).

Photochemical addition of a formamide molecule onto the double bond of the 3-(β -D-ribofuranosyl)acrylic ester **76** gave the succinamic ester **77** that cyclized and de-*O*-protected to a mixture of (*R*)- and (*S*)-dihydroshowdomycin (**78**) (80MI11) (Scheme 13).

Reaction of phenylthio- β -D-ribofuranoside acetate **79** with dimethyl diazomalonate gave **80**, which was elaborated to the α -keto ester **45** and then to showdomycin acetate **83** (87JA3010) (Scheme 14).



SCHEME 13



DABCO = 1,4-Diazabicyclo [2.2.2] octane

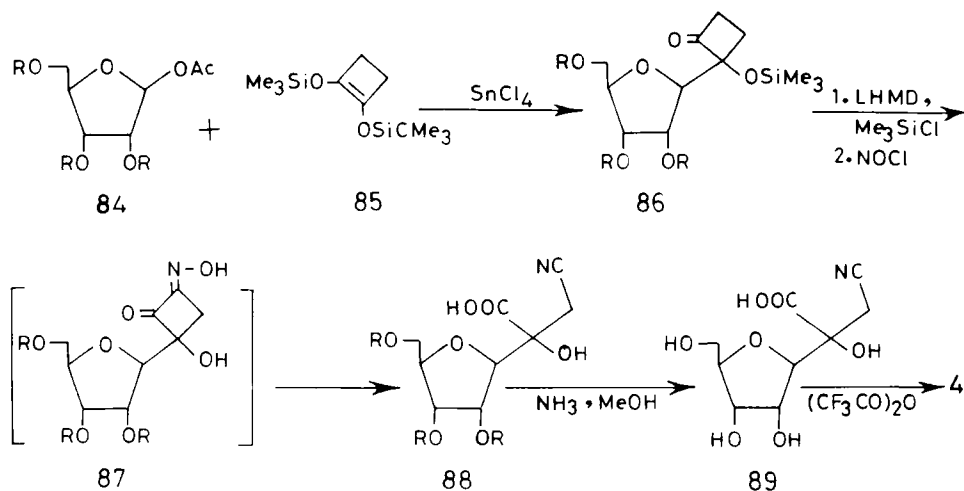
SCHEME 14

A synthetic approach in which the four carbons of the maleimide residue were joined to the ribofuranosyl moiety in a single step involved the C-glycosylation of the ribose derivatives **84** with 1,2-(trimethylsilyloxy) cyclobut-1-ene **85** to give **86**. Nitrosation of **86** gave the oxime **87** that underwent spontaneous cyclobutane ring cleavage to give the 3-cyano-2-hydroxy-2-(β -D-ribofuranosyl)propionic acid **88**. Removal of the *O*-protective groups followed by acid-catalyzed cyclization of **89** gave showdomycin (**4**) [80JCS(CC)251] (Scheme 15).

Synthesis of showdomycin (**4**) by carbon-carbon bond formation between the D-ribose and maleimide subunits usually lacks stereospecificity and affords a mixture of **4** and its α anomer **94**. Thus, reaction of unprotected D-ribose (**90**) with the maleimide-derived Wittig reagent **91** gave the unsaturated nucleoside **92** that was cyclized by the introduction and removal of a phenylseleno group to give a mixture of **4** and **94**; the latter preponderated (84JOC3673; 86JOC495) (Scheme 16).

Coupling 2-deoxy-D-ribose (**95**) and *N*-triphenylmethylmaleimide (**96**) in the presence of tributylphosphine gave a mixture of 2'-deoxyshowdomycin (**58**) and its α anomer (**59**) (93MI3) (Scheme 17).

Free radical coupling of *S*-methyl 1-(β -D-ribofuranosyl)dithiocarbonate (**97**), as ribofuranosyl radical precursor, and *N*-ethylmaleimide (**98**) gave a mixture of the α and β -dihydro-*N*-ethyl showdomycins **99** (88TL351) (Scheme 18).

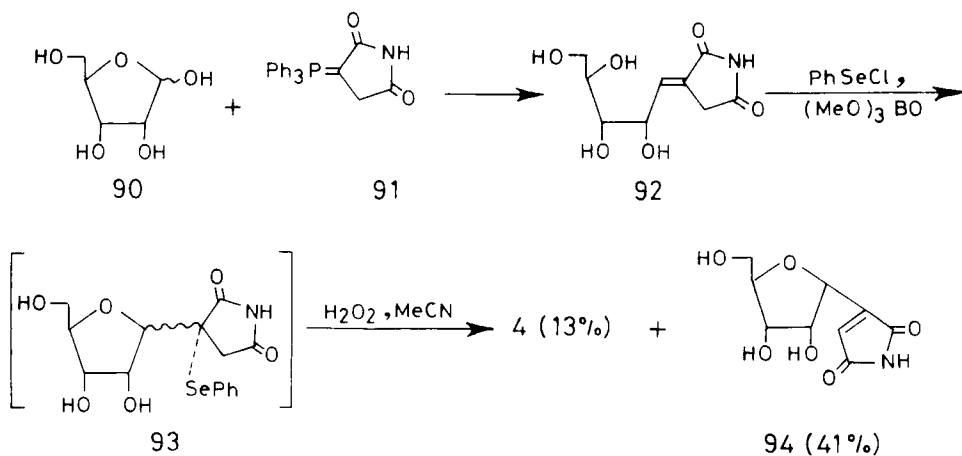


R = PhCO

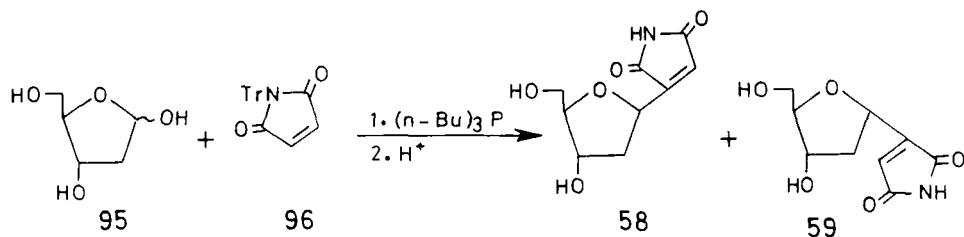
LHMD = Lithium hexamethyldisilazide

SCHEME 15

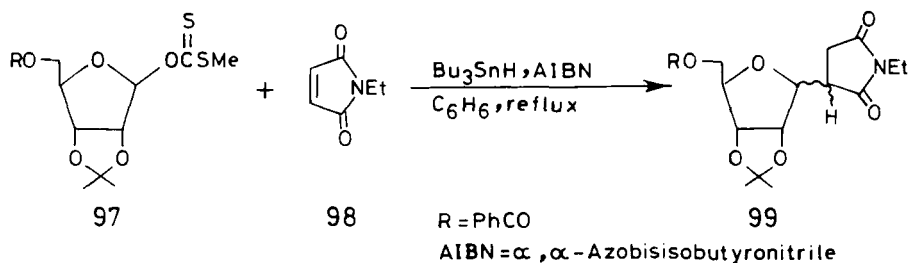
The β -anisyltelluro-D-ribofuranoside (**101**) photolytically generated the corresponding ribofuranosyl free radical, which stereoselectively coupled with maleimide to give, after dehydrogenation and de-*O*-protection, showdomycin (**4**) (90JA891) (Scheme 19).



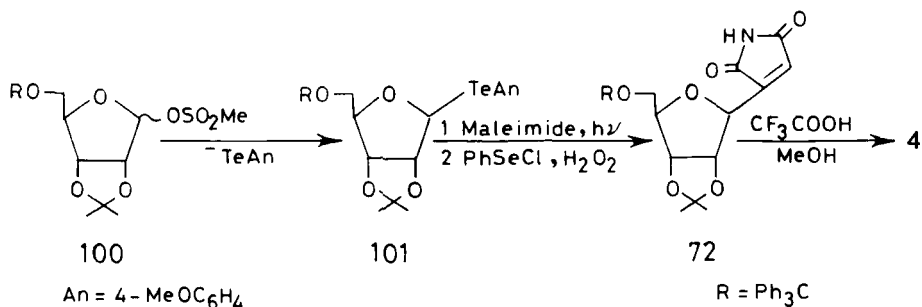
SCHEME 16



SCHEME 17



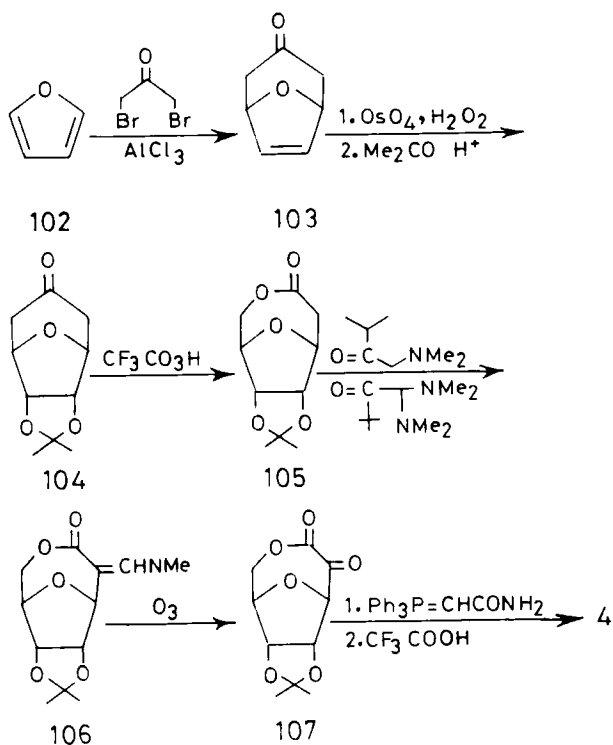
SCHEME 18



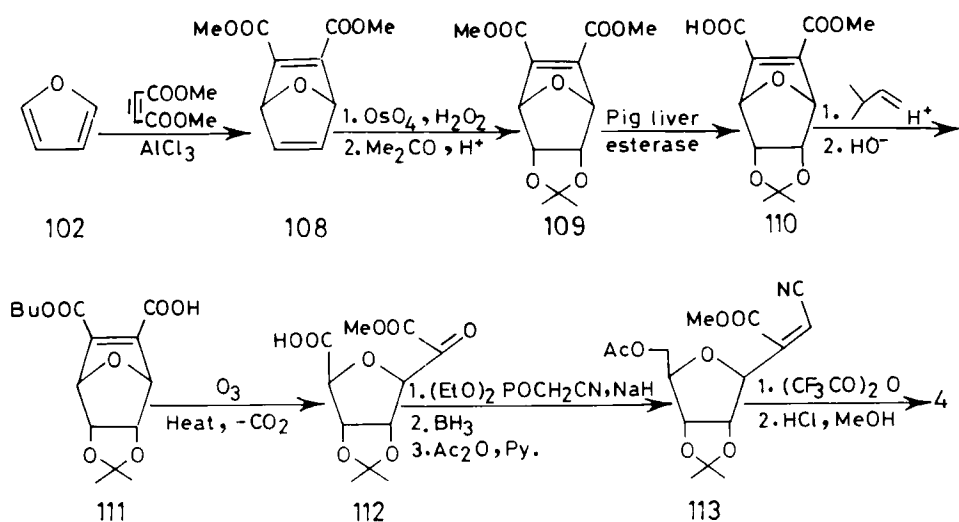
SCHEME 19

Noyori *et al.* utilized the rigid bicyclic ketone **103** for the total synthesis of showdomycin (**4**). The rigidity of the bicyclic system secured efficient stereochemical control throughout the overall transformations shown in Scheme 20 (78JA2561, 78TL1829; 80CJC2024; 84BCJ2515).

Another total synthetic plan to obtain showdomycin (**4**) was that which started from the Diels–Alder adduct **108** and comprised the key step of enzymatic hydrolysis of the diester **109** to the half ester **110** (81JA6739) (Scheme 21).



SCHEME 20



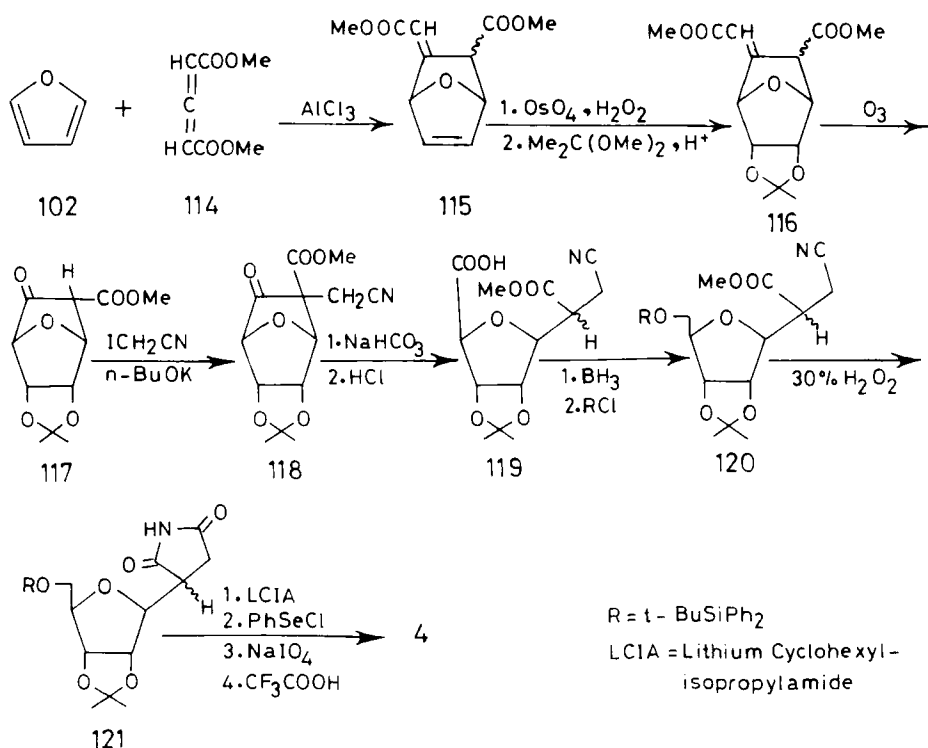
SCHEME 21

The 3-cyano-2-(1,4-anhydro-D-*ribo*-uronoyl)propanoate derivative **119**, a key intermediate in the total synthesis shown in Scheme 22, was obtained by reaction of **117** with iodoacetonitrile followed by opening of the bicyclic system of **118** (81JA3923).

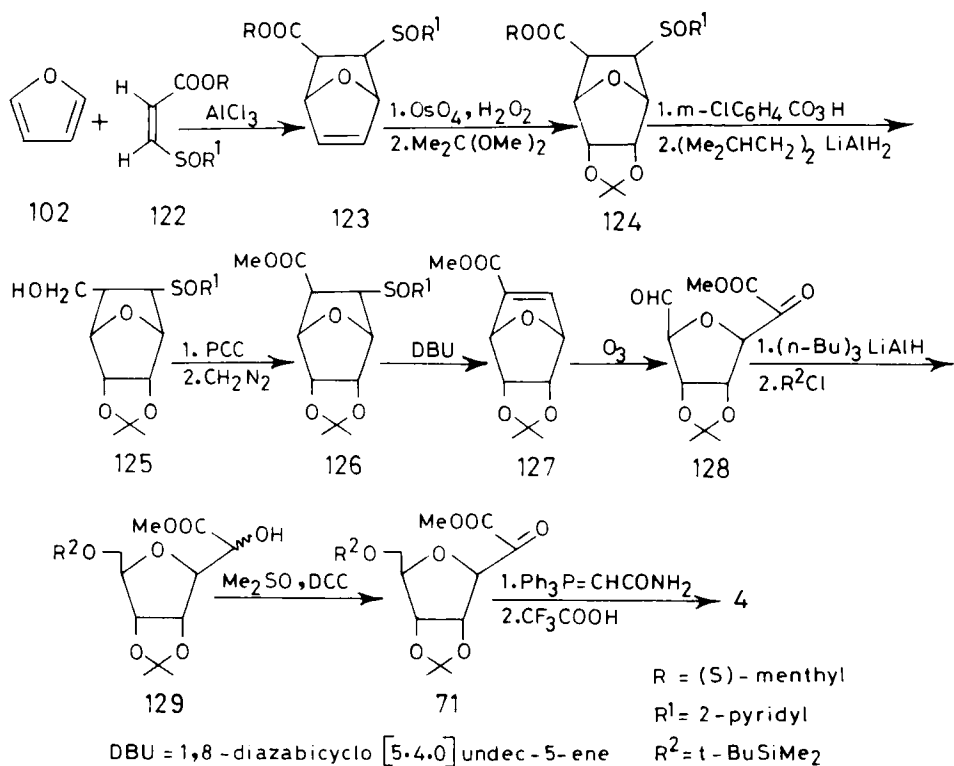
A highly enantioselective sequence of reactions was designed to prepare the key intermediate **127** from the asymmetric Diels–Alder adduct **123** resulting from addition of furan (**102**) to the asymmetric dienophile menthyl (*S*)-3-(2-pyridylsulfinyl)acrylate (**122**). Compound **127** was then elaborated to give showdomycin (**4**) (87CPB433) (Scheme 23).

DL-2'-Deoxyshowdomycin (**58**) was totally synthesized starting from the cycloaddition product **130** of furan (**102**) and methyl 2-nitroacrylate as shown in Scheme 24 (77CJC2993).

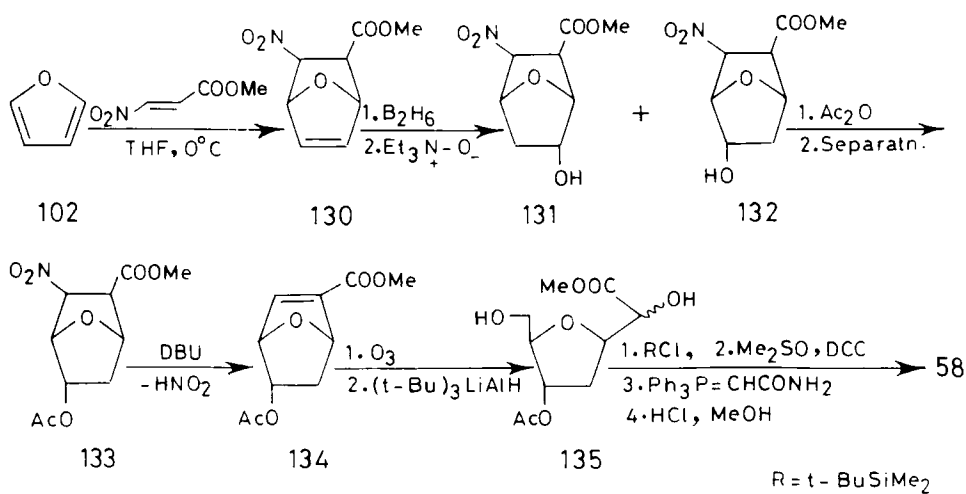
The showdomycin analog **142** in which the sugar ring oxygen is replaced by an *N*-carbomethoxy group was prepared from the tropanone derivative **136** as detailed in Scheme 25 (77CJC2998). This analog (**142**) failed to exhibit antimicrobial or antiviral activity, an indication of the key role of



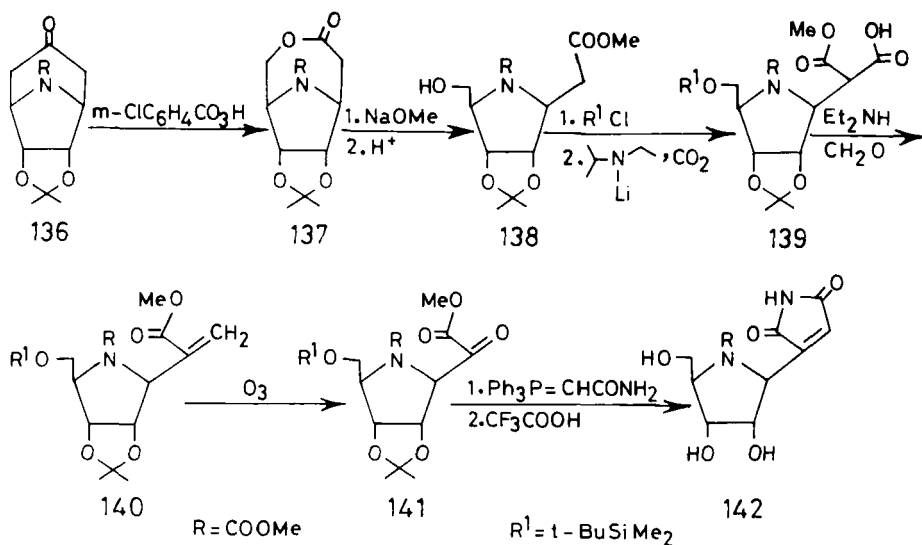
SCHEME 22



SCHEME 23



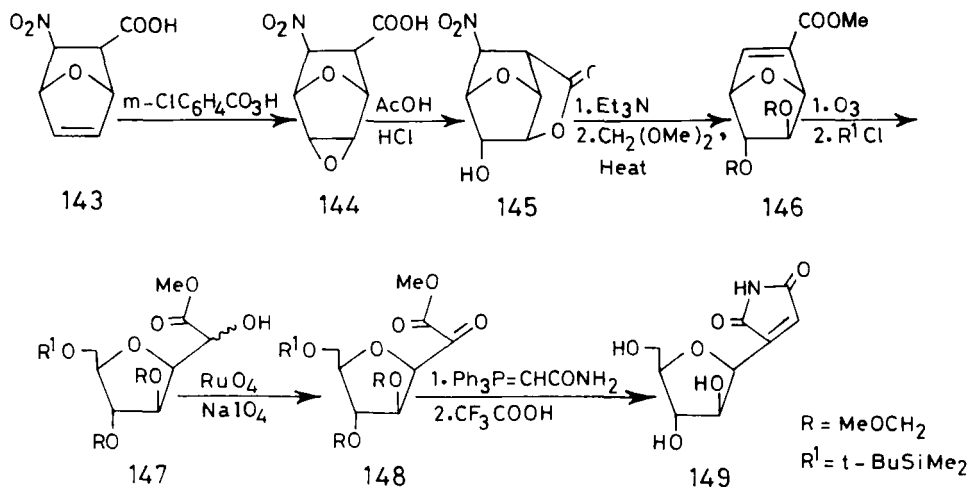
SCHEME 24



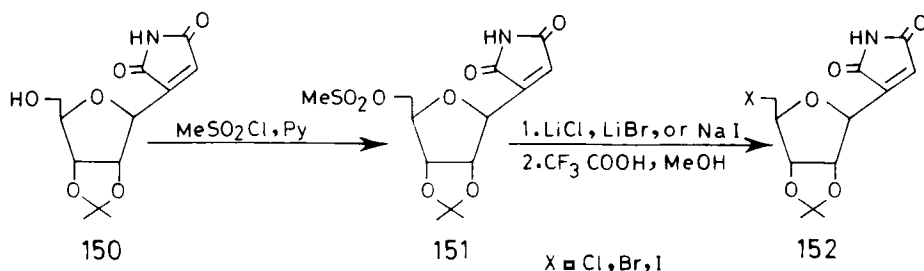
SCHEME 25

the sugar ring oxygen of showdomycin (**4**) in possessing biological activities (77CJC2998).

The total synthesis of 2-(β-D-arabinofuranosyl)maleimide (*ara*-showdomycin) (**149**) was accomplished from the bicyclic system **143** as given in Scheme 26 (80CJC2024).



SCHEME 26



SCHEME 27

Finally, the approach of transforming a C-nucleoside to another was applied to prepare 6'-deoxy-6'-haloshowdomycins (**152**) from 2', 3'-O-isopropylidene showdomycin (**150**) (78MI14) (Scheme 27).

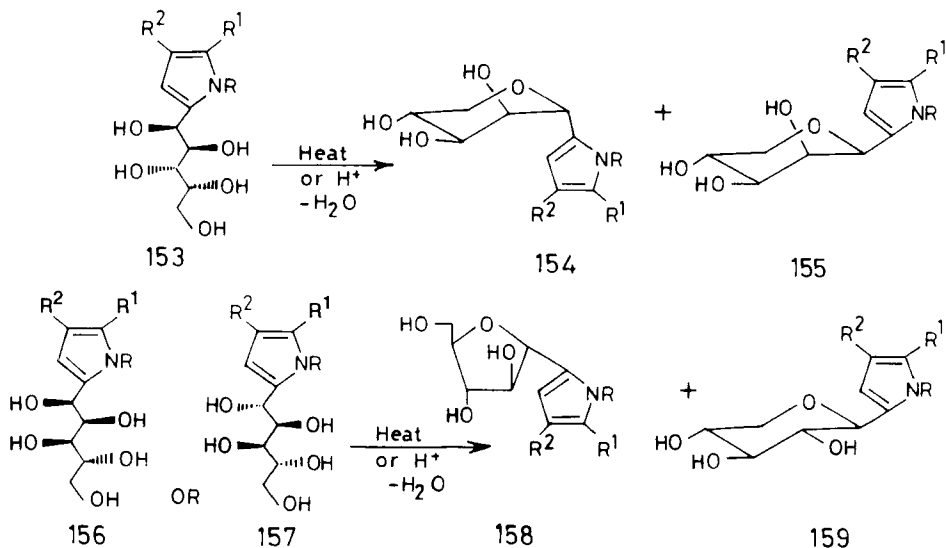
B. PYRROLE C-NUCLEOSIDES

1. 2(5)-Pyrrolyl C-Nucleosides

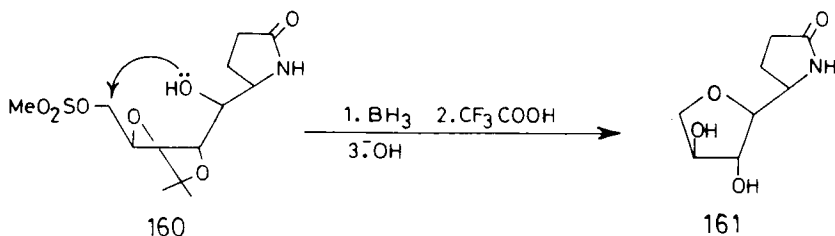
Cyclodehydration of alditolyl chains of pyrrol-2-yl acyclo C-nucleosides or their partially O-protected derivatives by heating in vacuum [50AQ(B)73], by heating in acid solutions [79AQ745; 82MI9; 85MI5; 86AQ(C)76; 87AQ(C)271; 92T5619; 95S638], or by treatment with triphenylphosphine and diethyl azodicarboxylate [95JAP(K)95/118268] gave pyrrol-2-yl C-nucleosides with furanose or pyranose sugar rings, depending on the configuration of the alditolyl chain and reaction conditions. It has been found that 2-(α - and β -*lyxo*-pyranosyl)pyrroles (**154** and **155**) were invariably obtained from 2-(*D-galacto*-pentitol-1-yl)pyrroles (**153**), whereas 2-(α -*D-arabinofuranosyl*)pyrroles (**158**) and 2-(α -*D-arabinopyranosyl*)pyrroles (**159**) were obtained from 2-(*D-gluco*- or *D-manno*-pentitol-1-yl)pyrroles (**156** and **157**) [87AQ(C)271] (Scheme 28). Cyclization of the derivatized 2-(alditol-1-yl)pyrrole **160** took place through intramolecular $\text{S}_{\text{N}}2$ attack of the C2' hydroxyl on the backside of C5' methylsulfonates to give **161** [93JCS(P1)2291] (Scheme 29).

Coupling 2-diethylalumino-1-methylpyrrole (**163**) with α -*D*-glycofuranosyl fluorides (**162**) afforded the corresponding pyrrol-2-yl C-nucleosides **164**, which retained the configuration of the anomeric center of the starting fluoride. β -*D*-Glycopyranosyl fluorides behaved similarly (88JOC3371) (Scheme 30).

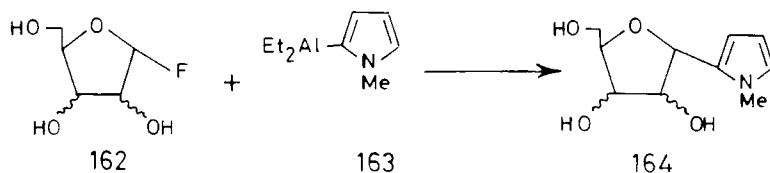
Transformation of 5-(β -*D*-ribofuranosyl)furan derivatives **166** to 2-(β -*D*-ribofuranosyl)pyrroles (**170**) was achieved by thermal rearrangement of



SCHEME 28



SCHEME 29

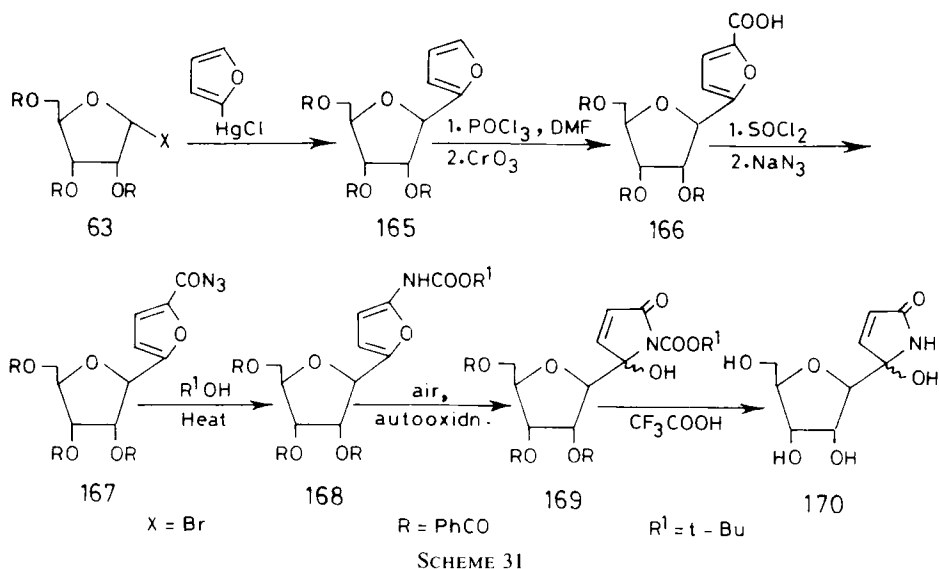


SCHEME 30

the acyl azide **167** in the presence of *tert*-butyl alcohol followed by autooxidation of the resulting carbamate **168** to **170** [87JOC2368, 87JOC4521; 88JOC1401; 89JCS(P1)649] (Scheme 31).

2. 3(4)-Pyrrolyl C-Nucleosides

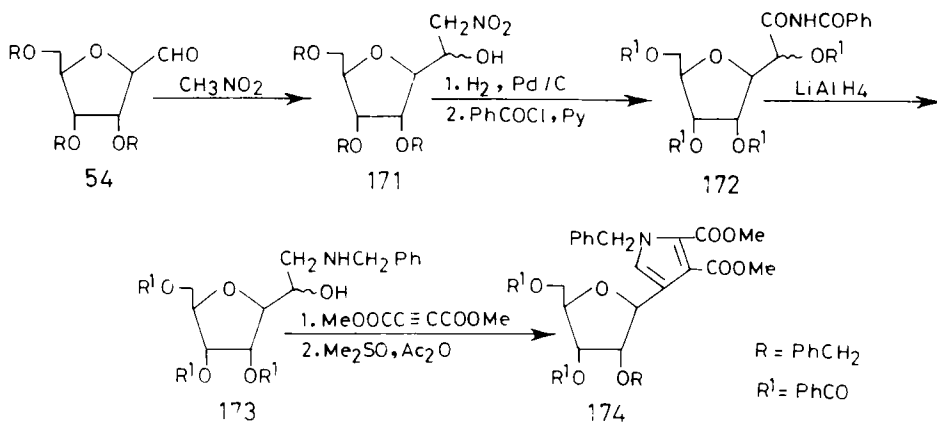
Dimethylacetylene dicarboxylate reacted with the *N*-benzyl 2-(β -D-ribofuranosyl)ethanolamine derivatives **173** to provide the two carbons

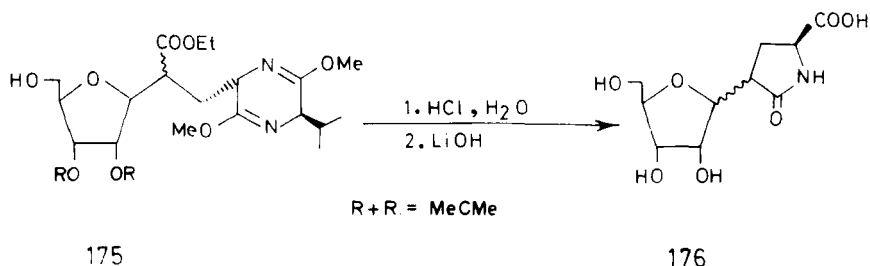


sary to complete the carbon skeleton of nucleoside **174** (78MI6) (Scheme 32).

Hydrolysis of the two imidate bonds of the pyrazine ring in the pyrazine homo *C*-nucleoside **175** (Section XXVI,B; Scheme 290) and cyclization of the product gave a mixture of the two anomeric 3-pyrrolyl *C*-nucleosides **176** [88TL375; 89JAP(K)89/29393] (Scheme 33).

Some pyrrole *C*-nucleosides were reported to possess antiviral and antitumor activities [89JAP(K)89/29393].





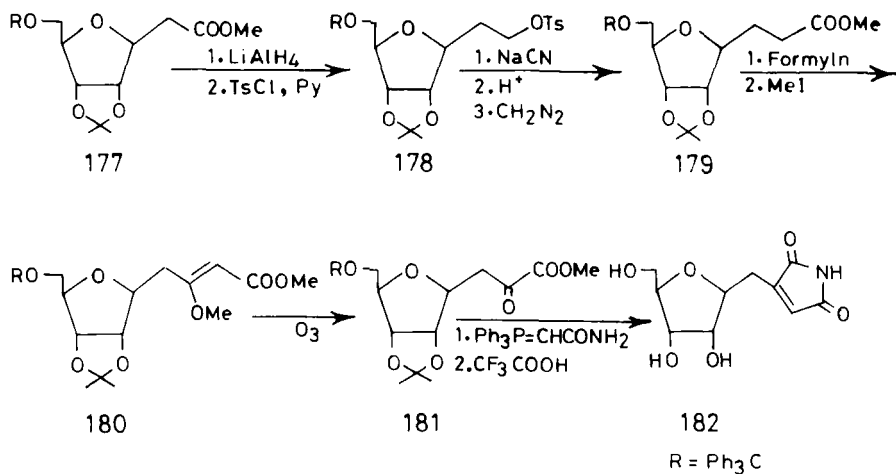
SCHEME 33

C. PYRROLE HOMO C-NUCLEOSIDES

1. 3(4)-Pyrrolyl Homo C-Nucleosides

Homoshowdomycin (**182**) was synthesized (79H141, 79MI3) from the previously mentioned bicyclic lactone **107** using the same reaction steps presented in Scheme 20 for the preparation of showdomycin.

Homoshowdomycin (**182**) has also been synthesized from the *C*- β -D-ribofuranosylacetic ester **177** through side-chain elongation to the 4-glycosyl-3-methoxybut-2-enoate **180**, then to the 3-glycosyl-2-oxopropanoate **181**, and finally to **182** (83BCJ2700) (Scheme 34).



SCHEME 34

D. PYRROLE CARBOCYCLIC C-NUCLEOSIDES

1. 3(4)-Pyrrolyl Carbocyclic C-Nucleosides

Aiming to compare the biological activities of showdomycin (**4**) with its carbocyclic analog **186** (carbашowdomycin), Just and Kim synthesized the latter from the bicyclo[2.2.1]heptane derivative **183** according to the total synthetic approach shown in Scheme 35 (76TL1063). Two comparable synthetic protocols of **186** have been reported by Japanese investigators (81TL5227; 91TA1035). Replacement of the sugar ring oxygen of showdomycin (**4**) by a methylene group in carbашowdomycin led to virtually complete loss of antiviral, antibacterial, and antifungal activities (76TL1063), an additional proof of the important role of the sugar oxygen of showdomycin in biological activity.

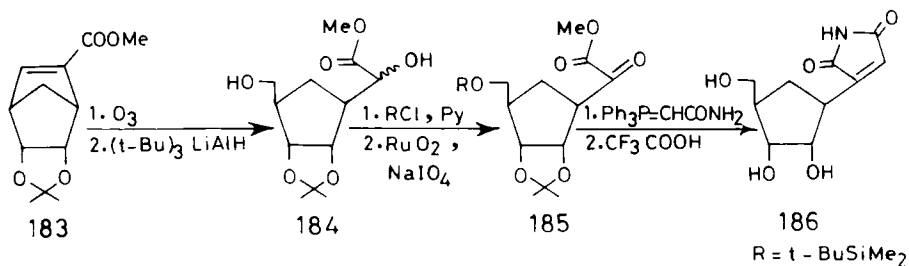
E. PYRROLE REVERSE C-NUCLEOSIDES

1. 2(5)-Pyrrolyl Reverse C-Nucleosides

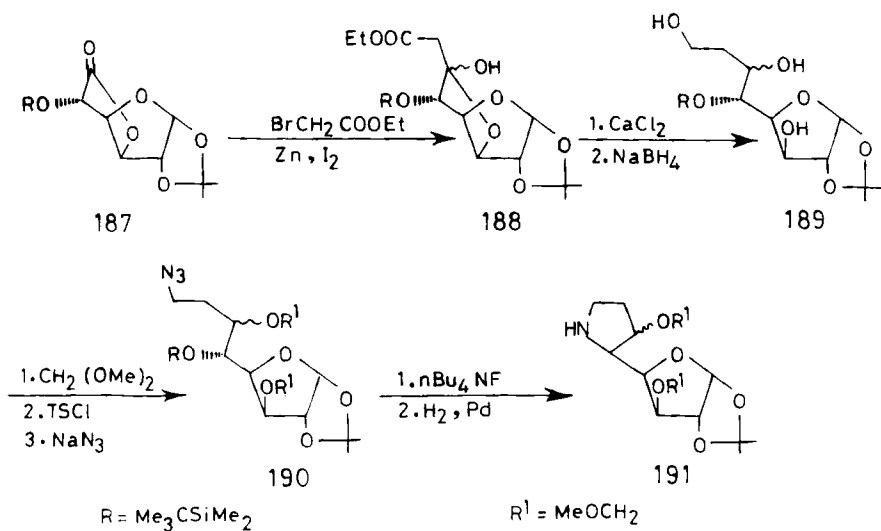
Chain extension at C6 of the D-glucouono-3,6-lactone derivative (**187**) by Reformatsky reaction gave the ester **188**, which was transformed to the pyrrole reversed C-nucleoside **191** (93LA379) (Scheme 36).

The reverse showdomycin analog **193** was synthesized by assembling its maleimide unit at the tail of the D-ribo-hexulofuranuronamide derivative **192** (89MI8) (Scheme 37). The D-xylo-congener of **193** has also been prepared by the same synthetic pathway (89MI8).

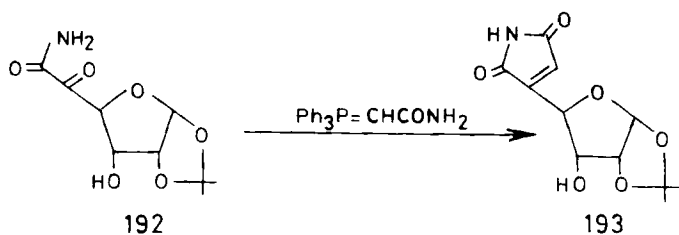
The aldehyde function of **195** regiospecifically condensed with position 2 of pyrrole in the presence of tin(IV) chloride to furnish the 5', 5'-di(pyrrol-2-yl) reverse C-nucleoside **196** (95JOC4964) (Scheme 38).



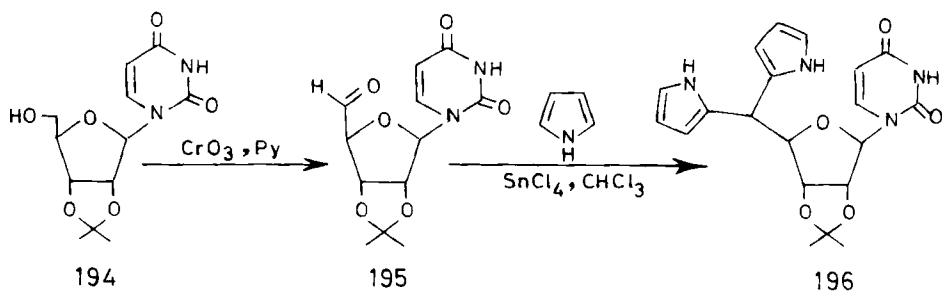
SCHEME 35



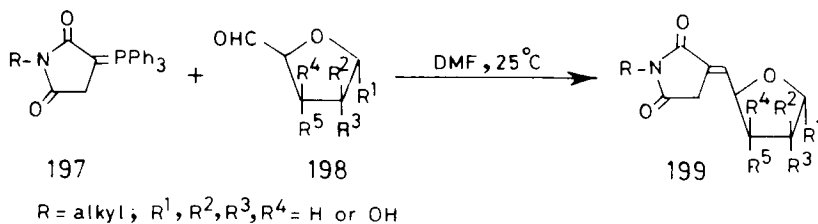
SCHEME 36



SCHEME 37



SCHEME 38



SCHEME 39

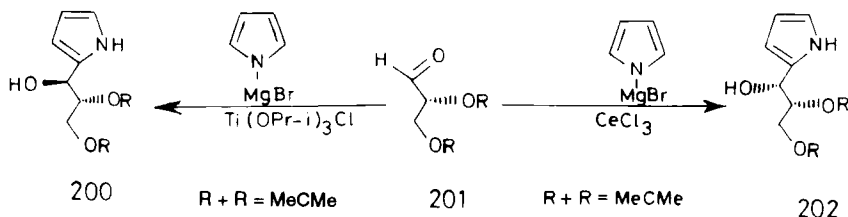
2. 3(4)-Pyrrolyl Reverse C-Nucleosides

A series of reverse 3-(glycosylidene)succinimides (**199**) were prepared by condensation of the aldehyde-sugar derivatives **198** with succinimide-nephosphoranes (**197**) (79HCA977, 79HCA2788) (Scheme 39). Some of these compounds were active against lymphocytic leukemia P388, probably because of their alkylating properties (79HCA977). They also showed limited but significant antiviral activity against herpes virus type 1 (HF) (79HCA2788).

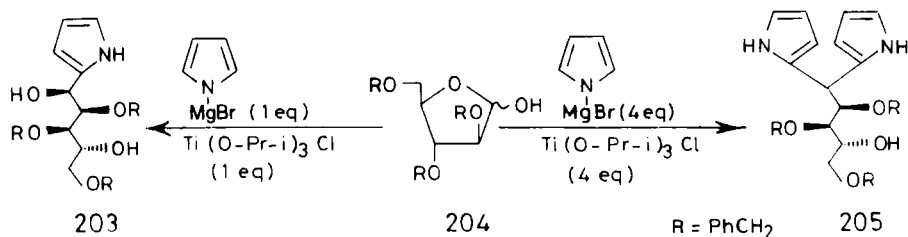
F. PYRROLE ACYCLO C-NUCLEOSIDES

1. 2(5)-Pyrrolyl Acyclo C-Nucleosides

Divergent diastereoselective metal-assisted heteroarylation of sugars at C1 with position 2 of pyrrole has been made possible by tuning the pyrrole metal system (92T5619). Thus, reaction of 1-pyrrolyl magnesium bromide with 2,3-*O*-isopropylidene-D-glyceraldehyde (**201**) in the presence of triisopropoxytitanium chloride gave, predominantly, the 2-(D-*erythro*-glycerol-1-yl)pyrrole derivative **200**. Carrying out the same reaction in the presence of cerium(III) chloride diverted the diastereoselectivity to the D-*threo*-counterpart **202** (92T5619) (Scheme 40). Reaction of the Cl unprotected



SCHEME 40



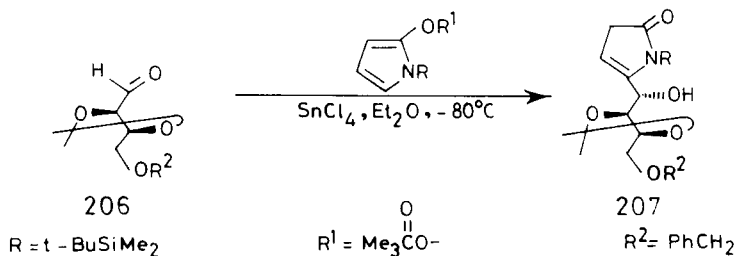
SCHEME 41

sugar derivative **204** with one equivalent of 1-pyrrolylmagnesium bromide in the presence of the titanium salt diastereoselectively gave the 2-(*D*-manno-pentitol-1-yl)pyrrole (**203**) (92T5619). Performing this reaction with four equivalents of 1-pyrrolylmagnesium bromide and the titanium salt gave the 1,1-di(pyrrol-2-yl)alditol **205** (92T5619) (Scheme 41). A similar ribosylation of 1-pyrrolylmagnesium bromide has recently been reported (91T5339).

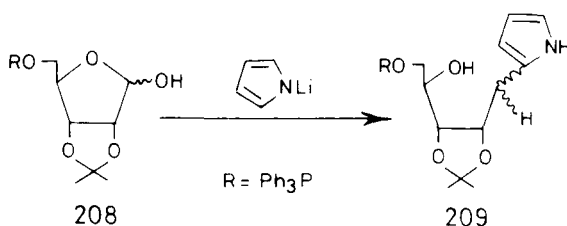
aldehydo-Sugar derivatives such as **206** also regiospecifically coupled with pyrrole derivatives in the presence of tin(IV) chloride to afford the corresponding 2-(alditol-1-yl)-pyrroles **207** [93JCS(P1)2291] (Scheme 42).

Coupling the Cl unprotected *D*-ribofuranose derivative **208** [95JAP(K)95/118268] or an analogous derivative of 2-deoxy-*D*-ribose (95S638) with 2-lithiopyrrole gave a mixture of the two stereoisomeric pyrrol-2-yl acyclo *C*-nucleosides **209** (Scheme 43).

Synthesis of pyrrol-2-yl acyclo *C*-nucleosides by forming the pyrrole ring onto the alditolyl chain was reported in 1922, when Pauly and Ludwig prepared 3-ethoxycarbonyl-2-methyl-2-(*D*-arabino-tetritol-1-yl) pyrrole (**211**), the first example of these compounds, by reaction of 2-amino-2-deoxy-*D*-glucose (**210**) with ethyl acetoacetate (22ZPC170) (Scheme 44). Since then, Spanish chemists have pioneered the synthesis of these compounds using this route and extensively studied their properties and mecha-



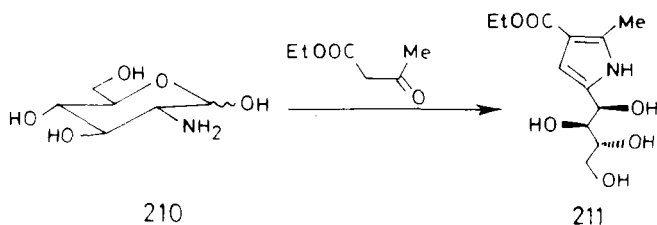
SCHEME 42



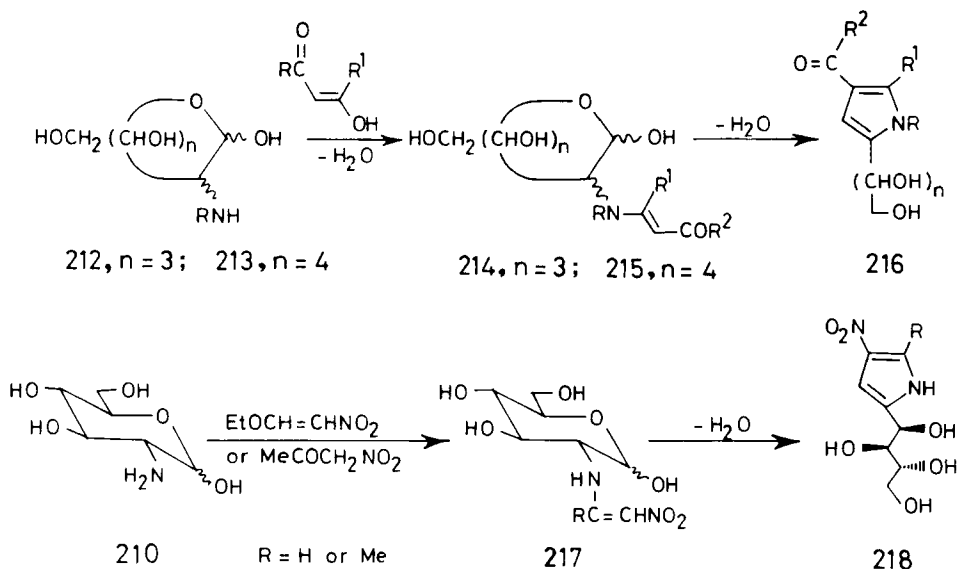
SCHEME 43

nism of formation, as well as reviewing their chemistry (56MI1; 65MI2). Synthesis of these compounds has also been briefly reviewed, together with that of other heterocyclic derivatives of carbohydrates (70MI1). Cyclocondensation of 2-amino-2-deoxyaldohexoses (**212**) [61AF(Q)B383; 67MI3; 71AQ383; 71MI3; 74AQ1082; 83AQ(C)317; 84MI5; 90MI6] or 2-amino-2-deoxyaldohexoses (**213**) [79AQ756; 86AQ(C)76; 87AQ(C)271] with various 1,3-dicarbonyl compounds took place through the isolable enamine intermediates (**214** and **215**) [63BJ(88)132; 65MI6; 67MI3] to give the corresponding 2-(alditol-1-yl)pyrroles **216** (Scheme 45). Since, in these reactions, one of the two acyl groups of the 1,3-dicarbonyl compound remains unchanged and serves only to activate the contiguous methylene group, it was concluded that aldehydes or ketones possessing an electron-withdrawing group in the β -position to their carbonyl group would lead to a similar reaction outcome. This conclusion was justified by finding that 3-nitro-5-(alditol-1-yl)pyrroles **218** were obtained from the reaction of 2-amino-2-deoxy-D-glucose (**210**) with 1-ethoxy-2-nitroethene (equivalent to nitroacetaldehyde) (87MI4) or nitroacetone (89MI9) (Scheme 45). Some of the latter nitropyrrole acyclo C-nucleosides have also been obtained by direct nitration of the parent compounds, a disadvantageous procedure that produced mixtures of isomers [85AQ(C)49].

Addition of dimethyl acetylenedicarboxylate to 2-amino-2-deoxy-D-glucose (**210**) gave the intermediate enamine **219**, which cyclized to the 2-(alditol-1-yl)pyrrole **220** (74MI2) (Scheme 46).



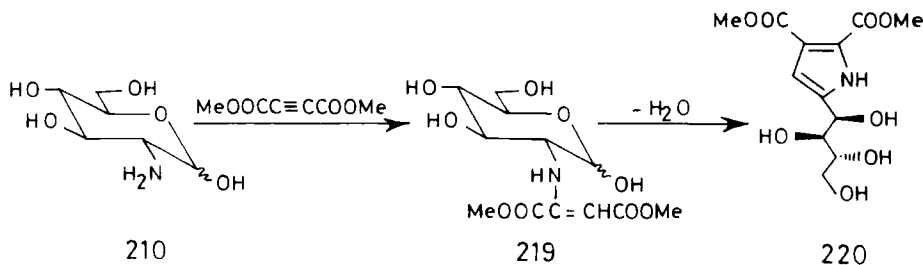
SCHEME 44



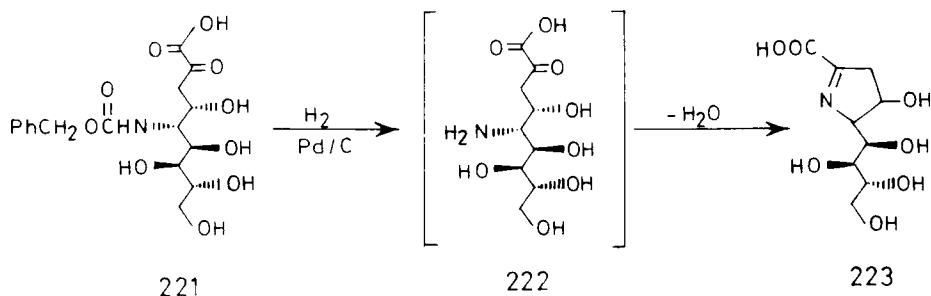
SCHEME 45

2(5)-Pyrrolyl acylo *C*-nucleosides were formed upon generation of an amino function in a proper position relative to another group, on a sugar molecule, with which it can cyclize to form the pyrrole ring (67ZPC378; 93JOC264, 93MI9; 94TL8973). An illustrative example is the hydrogenolysis of *N*-benzyloxycarbonyl-neuraminic acid (**221**) to give the 2-pyrrolyl acylo *C*-nucleoside **223** as a result of intramolecular cyclodehydration of **222** (67ZPC378; 93JOC264) (Scheme 47).

Displacement of the methylsulfonyloxy group of the 2-deoxy-D-octitol derivative **224** with benzylamine occurred with simultaneous cyclodehydra-



SCHEME 46

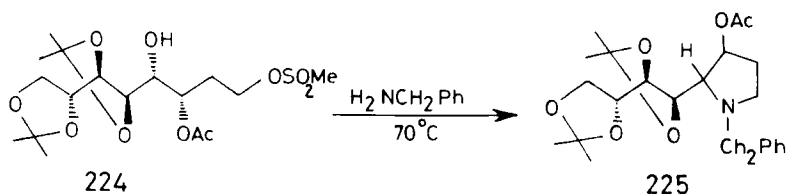


SCHEME 47

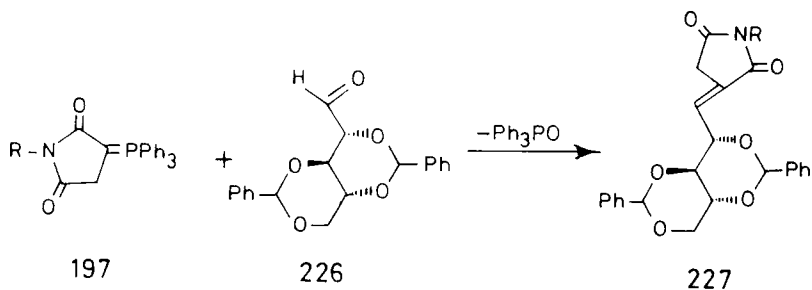
tion to produce the 2-(tetritol-1-yl)pyrrole derivative **225** (94TL8973) (Scheme 48).

2. 3(4)-Pyrrolyl Acyclo C-Nucleosides

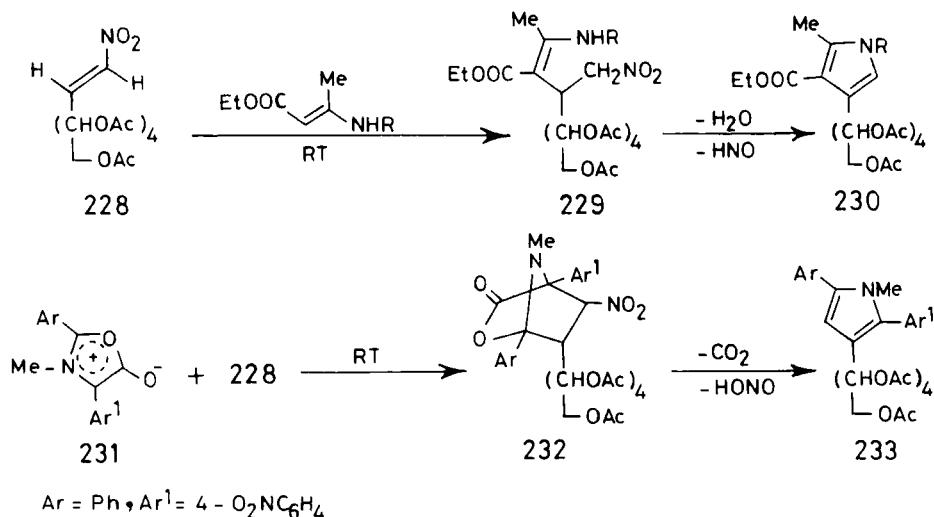
Direct heteroarylation of the acyclic D-ribose derivative **226** with the maleimide phosphorus ylides **197** gave the corresponding 3-(alditol-1-ylidene)pyrroles **227** (69MI7) (Scheme 49).



SCHEME 48

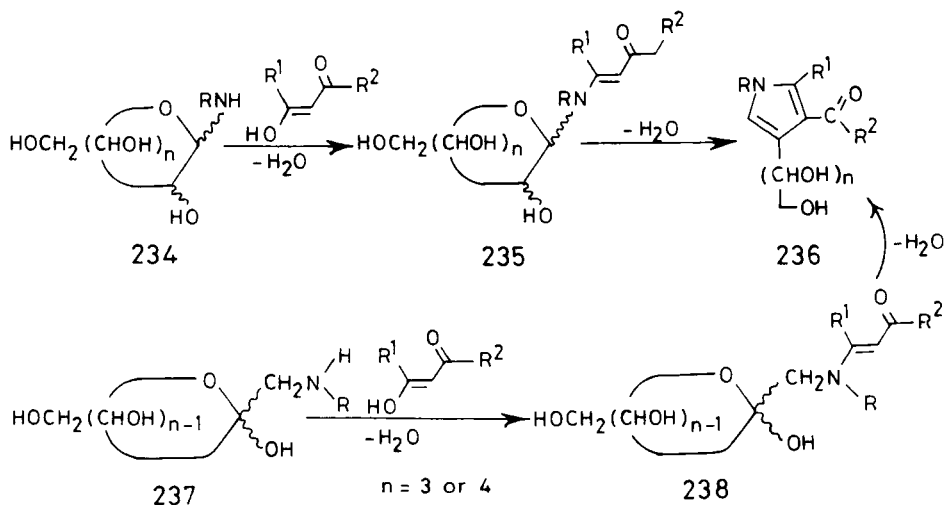


SCHEME 49

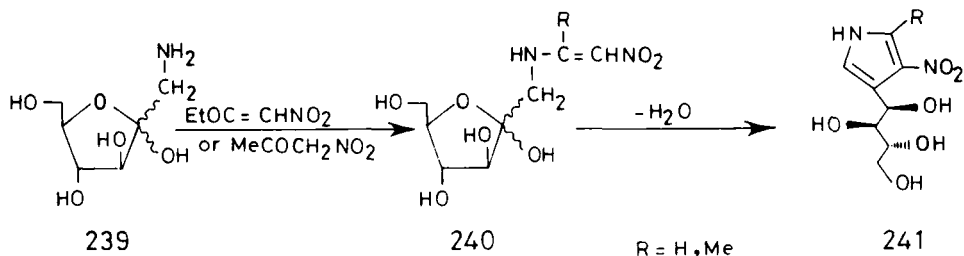


SCHEME 50

In two instances, 3-(poly-*O*-acetylalditol-1-yl)pyrroles were prepared by 1,3-dipolar cycloaddition of 2-(penta-*O*-acetylpenitol-1-yl)-1-nitroethene (**228**) as dipolarophiles to 3-(alkylamino)crotonic esters [80JCS(P1)1199] or to the mesoionic oxazolium olate **231** (89MI6) to give **230** and **233**, respectively (Scheme 50).



SCHEME 51



SCHEME 52

Condensation of glycosylamines (**234**) [58AFQ(B)753; 66MI3; 69MI5], 1-amino-1-ketohexoses (**237**, $n = 4$) [71AQ389; 72AQ571; 78AQ1281; 83AQ(C)317; 92MI6] and 1-amino-1-deoxyketoheptoses (**237**, $n = 5$) (76AQ855) with 1,3-dicarbonyl compounds gave the corresponding 3-(alditol-1-yl)pyrroles (**236**) through the often-isolated and well-identified 3-(glycosylamino)enone intermediates (**235** and **238**) (65MI6; 69MI5). In the case of unsymmetrical 1,3-dicarbonyl compounds, condensation usually takes place between the sugar amino function and the more enolizable carbonyl group (Scheme 51).

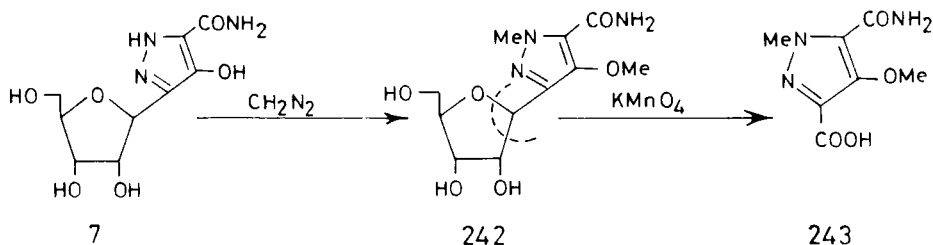
The 4-(alditol-1-yl)-3-nitropyrroles **241** were obtained from the reaction of 1-amino-1-deoxyketohexoses (**239**) with 1-ethoxy-2-nitroethene or nitroacetone (87MI4; 89MI9) (Scheme 52).

VII. 1,2-Diazole C-Nucleosides

Like azole C-nucleosides (Section VI), 1,2-diazole C-nucleosides and their analogs were also extensively studied from both the academic and the applied and medicinal chemistry points of view after the discovery of the naturally occurring C-nucleoside antibiotic pyrazofurin (**7**).

A. THE NATURALLY OCCURRING PYRAZOLE C-NUCLEOSIDE ANTIBIOTIC "PYRAZOFURIN" AND ITS CONGENERS

Chronologically, pyrazofurin (**7**) was the fourth isolated naturally occurring C-nucleoside. It has been isolated from the culture filtrates of *Streptomyces candidus* NRL3601 and christened "pyrazomycin" (69MI1; 72MI11; 74USP3802999). In 1976, the USAN adopted the name "pyrazofurin" instead of "pyrazomycin" (75ANY544). UV, IR, and ^1H NMR measurements,



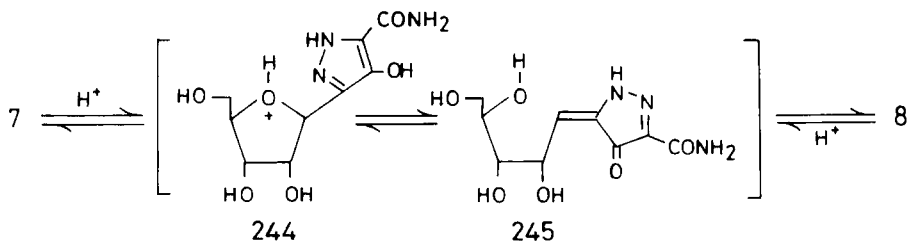
SCHEME 53

and methylation with diazomethane followed by oxidation to the pyrazole carboxylic acid derivative **243**, established the 5-carboxamido-4-hydroxy-3-(β -D-ribofuranosyl)pyrazole structure of pyrazofurin (**7**) (69MI1) (Scheme 53). The mass spectrum of **7** showed a peak corresponding to the structure of its pyrazole unit carrying a protonated formyl group ($B + 30$) (72TL2279) in addition to fragments characterizing the juxtaposition of the hydroxyl and carboxamido groups on the pyrazole ring (73JHC843).

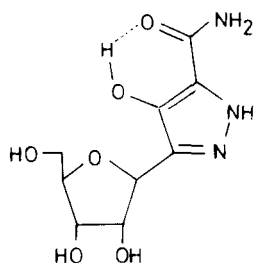
Pyrazofurin B (**8**), the α -anomer of pyrazofurin (**7**), was also isolated from culture filterates of the same microorganism [73BBR(51)312] and has been suggested to be produced as a result of acid-catalyzed anomerization of **7** through the intermediacy of the acyclic structure **245** (75ANY544) (Scheme 54).

X-ray crystallographic analysis of pyrazofurin (**7**) (72MI2) and ^{13}C NMR spectrometry [73BBR(51)318] pinpointed its syn-conformation and the existence of strong intramolecular hydrogen bonding between the pyrazole hydroxyl and carboxamide groups (**246**). The X-ray analysis of pyrazofurin B (**8**) revealed the tilting of its pyrazole ring so that a long hydrogen bond exists between the 4OH hydrogen and the 2'OH oxygen (**247**) [73BBR(51)312].

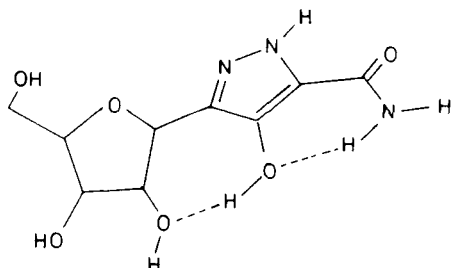
Studies on the biosynthesis of pyrazofurin using labeled nutrients in the fermentation media of *Streptomyces candidus* indicated that D-ribose and L-glutamate are its principal biosynthetic precursors [80JCS(CC)917].



SCHEME 54



246

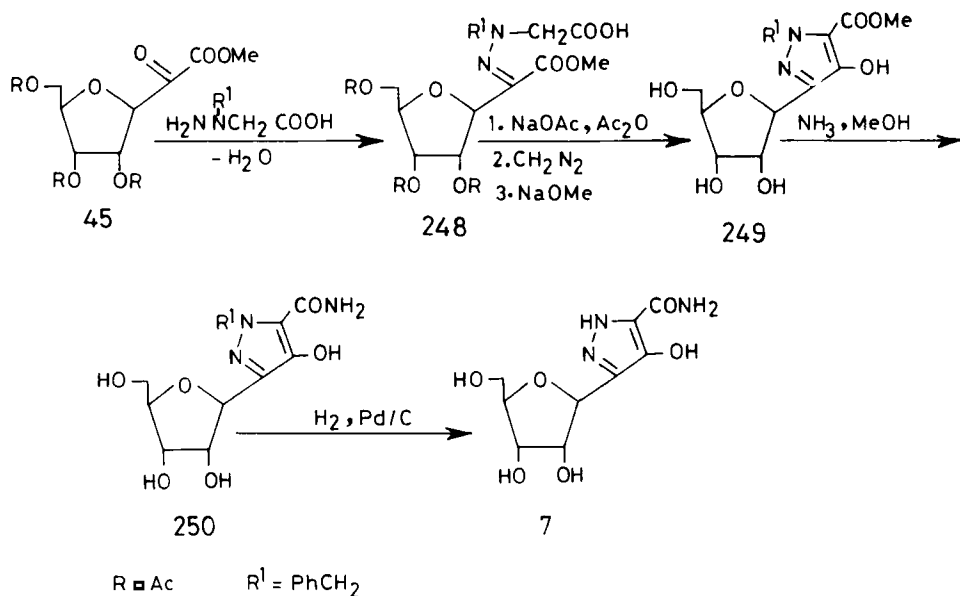


247

Pyrazofurin was found to possess antifungal activity against *Neurospora* (74USP3802999) and potent broad-spectrum antiviral activity (69MI3; 71PAC489; 76MI2; 82MI3). It is particularly active against pox-, picorna-, toga-, myxo-, and retroviruses (77ANY472; 78MI13), herpes simplex and smallpox viruses (74USP3802999), influenza viruses A–C (88AAC906), and respiratory syncytial virus (89MI3, 89MI4). In addition, pyrazofurin showed antitumor activities (74USP3802999; 76MI2; 78MI8); it completely inhibited the growth of Walker carcinoma and more than 50% growth of mammary carcinoma 755, Gardner lymphosarcoma, and X5563 plasma cell myeloma (73MI2). Unfortunately, pyrazofurin exhibited profound toxicity in mice (72MI2; 78MI13). Clinical trials as an antitumor agent in man (75ANY544; 77MI1, 77MI2; 78MI8) showed that it has side effects that limit its usage. In human blood cells, pyrazofurin is converted to the 5'-monophosphate by the cellular adenosine kinase (77MI3), and it has been pointed out that the biological activities of pyrazofurin are due to the inhibition of orotidylate decarboxylase (69MI3; 77MI4), aminoimidazole carboxamide ribonucleotide transformylase (78MI7), and purine biosynthesis (80MI4) by the 5'-monophosphate. On the molecular level, it has been suggested that the pyrazole C4 hydroxyl of pyrazofurin may be essential for its antileukemic activity against L1210 cells (75ANY544), a suggestion that has been confirmed by synthetic studies (76JHC1359). The toxicity of pyrazofurin analogs has recently been reviewed (94MI1).

The first published synthesis of pyrazofurin was that accomplished by Farkas, Fleglova, and Sorm (72TL2279) by condensation of the C-ribofuranosyl α -ketoester **45** with 1-benzylhydrazinoacetic acid to give the corresponding hydrazone **248**, followed by cyclization, amidation, and debenzylation to **7** (Scheme 55).

Pyrazofurin (**7**) and its α -anomer pyrazofurin B (**8**) were obtained upon diazotization of the 3-oxo-2-(α -D-ribofuranosyl)glutarate derivative **252** followed by cyclization and ammonolysis; prolonging the time of ammonolysis



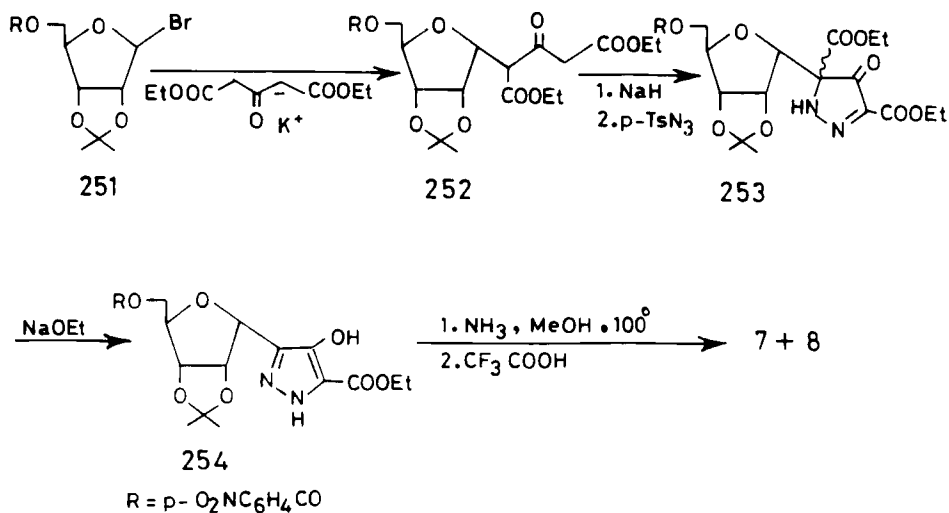
SCHEME 55

increased the yield of pyrazofurin (76JOC287, 76USP3998999) (Scheme 56). The ease of base-catalyzed anomerization of **254** indicated the probable involvement of a resonance-stabilized acyclic sugar intermediate similar to **245** (65B1710). 5'-Deoxypyrazofurin was prepared according to this protocol from the 5-deoxy analog of **252** (93JMC3727) and was found active against syncytial and vascular stomatitis virus in HeLA cells, vaccinia virus, and influenza A virus (93JMC3727).

The 3-oxo-4-(α , β -D-ribofuranosyl)butanoate derivative **255** has been used to synthesize **7** and **8** [82JCS(CC)664, 82MI6; 84JCS(P1)553; 85MI6] according to the steps shown in Scheme 57. The α - and β -D-mannofuranosyl analogs of **7** and **8** were also prepared from the D-mannofuranosyl analog of **255** (85MI4).

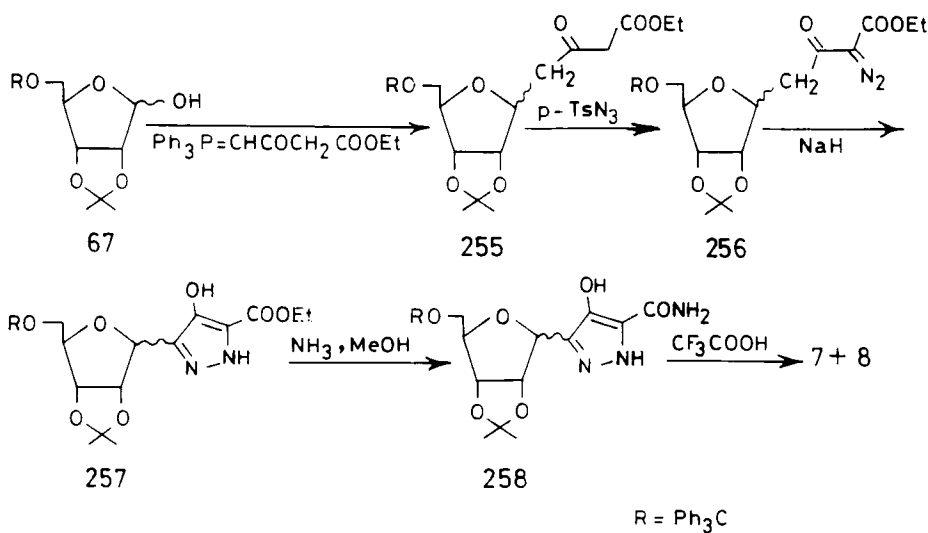
Synthesis from the β -D-ribofuranosylpropargaldehyde diethyl acetal derivative **259** is outlined in Scheme 58; the aminonitrile **264** was constructed [80CJC2624, 80JCS(CC)237] and then subjected to the key steps of transforming the amino and cyano functions to hydroxyl and carboxamido functions, respectively, under mild conditions [80JCS(CC)916; 81JCS(P1)2374].

In search of more biologically active but less toxic congeners of pyrazofurin, compounds **267–271** (76USP3960836; 77USP4053689; 86JMC268), as well as *O*-, *N*-, *O*-, *N*-acetyl, propyl, palmitoyl, and adamantoyl derivatives

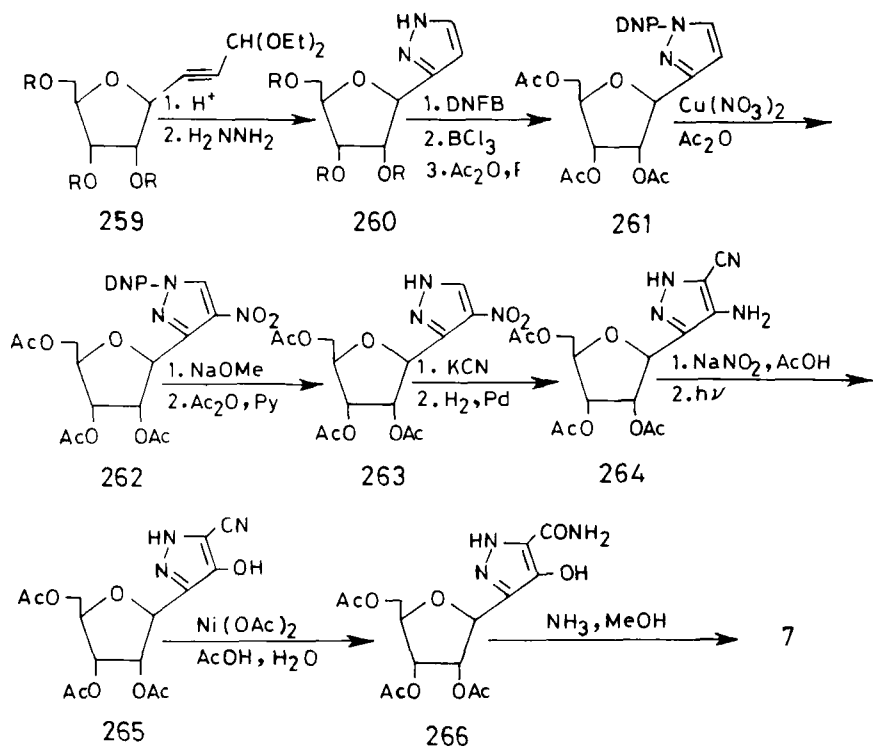


SCHEME 56

of pyrazofurin (76GEP2532069), were prepared. The antiviral activity of pyrazofurin 5'-phosphate (**270**) paralleled that of pyrazofurin, but **270** is much less toxic. Derivatives that are modified at positions 1, 4, or 5 showed neither antiviral nor cytostatic activity in cell culture (86JMC268).



SCHEME 57

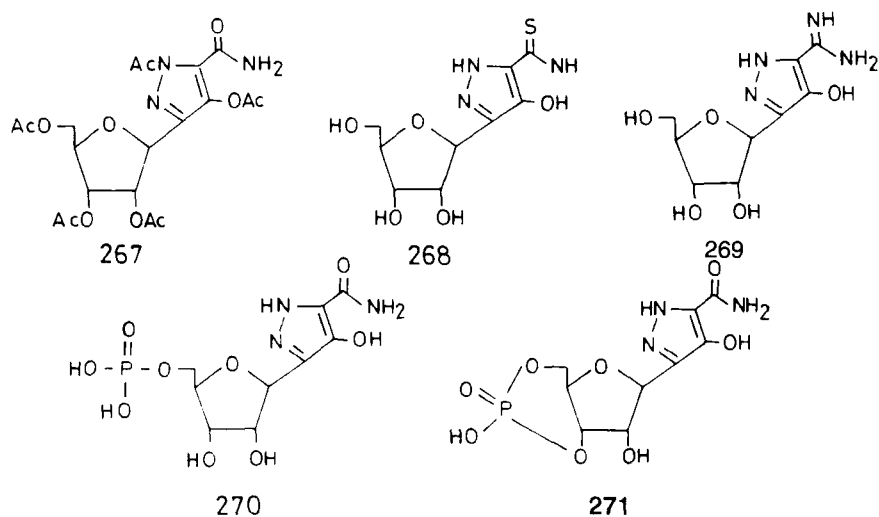


R = PhCH₂

DNFB =

DNP =

SCHEME 58

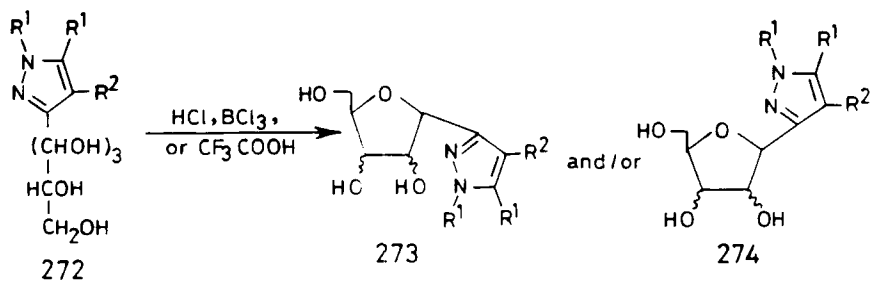


B. PYRAZOLE C-NUCLEOSIDES

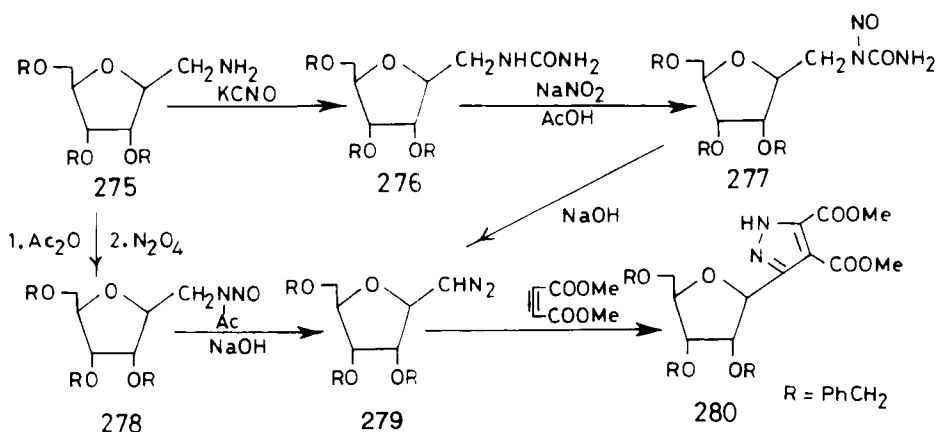
1. 3(5)-Pyrazolyl C-Nucleosides

Acid-catalyzed intramolecular cyclodehydration of 3-(D-pentitol-1-yl)pyrazoles having various pentitolyl chain configurations (**272**) was studied and found to give one or two 3-pentofuranosylpyrazole anomers (**273**, **274**) in varying proportions [79JCS(P1)244; 80JCS(P1)2561; 81JCS(P1)2258; 84T119; 86JCS(P1)1267; 90MI7; 91MI9; 93MI6]. These results were rationalized in terms of different reaction mechanisms (90MI7) as a result of different steric and electronic factors (93MI6) (Scheme 59).

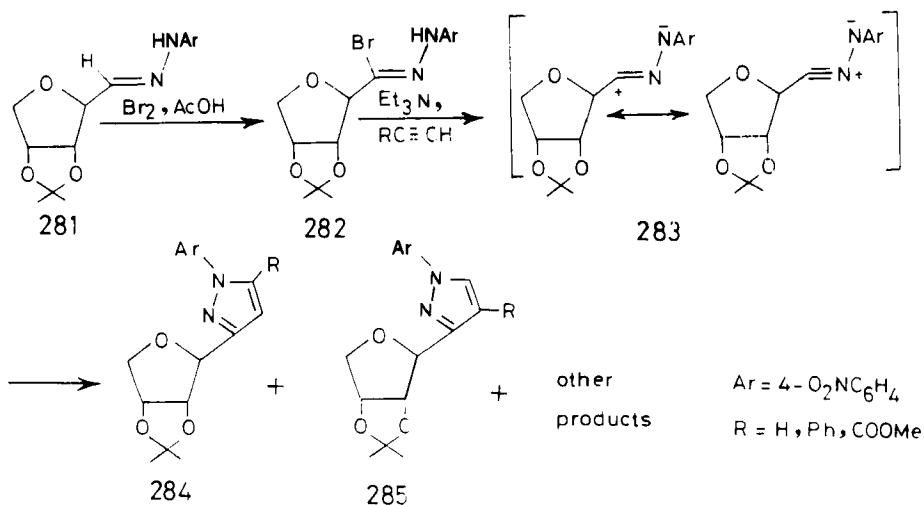
Many 3-(pentofuranosyl)pyrazoles (e.g., **280**) were prepared [70JCS(CC)313, 70TL4611; 71JCS(CC)986; 74MI1; 78MI16; 84JOC528; 93MI8] by 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate on C-glycosyldiazomethane derivatives such as **279** (Scheme 60).



SCHEME 59



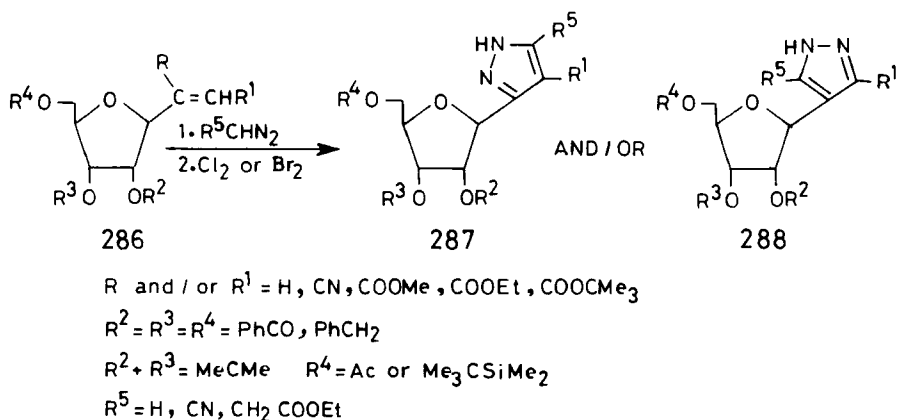
SCHEME 60



SCHEME 61

p-Nitrophenylhydrazonoyl halides of furanose (e.g., **282**) or pyranose sugars also undergo base-catalyzed 1,3-dipolar cycloaddition with alkynes to give 3-glycosylpyrazoles (**284**) (70HCA648; 71HCA683, 71HCA921, 71HCA1131; 72HCA2121). In one instance, the isolation of the two positional isomers **284** and **285** was reported (76MI8) (Scheme 61).

Diazoalkanes add to *C*-glycosylalkenes having a reactive double bond (**286**) to give 3- and/or 4-glycosylpyrazolines (74JOC2176; 75TL985; 88MI8) that can undergo elimination upon treatment with halogens to give the corresponding pyrazole *C*-nucleosides (**287**, **288**) (Scheme 62).

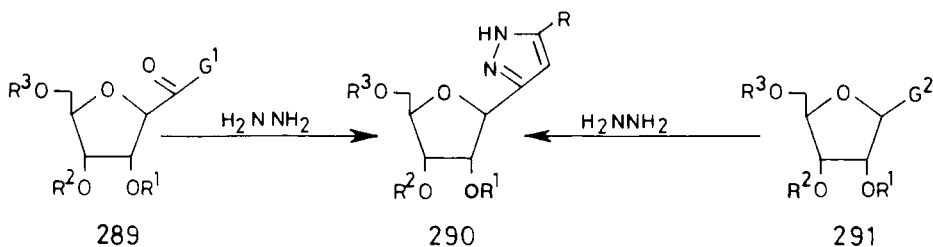


SCHEME 62

Hydrazine and its derivatives were used to provide the two contiguous nitrogens of the pyrazole ring by cyclocondensation with C-glycosyl derivatives **289** or **291**, which possess properly functionalized three-carbon side chains such as glycosylalkynyl ketone (80MI1; 82MI15), 3-glycosylpropyn-1-ylaldehyde [92JCS(P1)1573], glycosylethoxycarbonylmethyl ketone (83JOC1139), 3-glycosylproparginaldehyde [77JCS(P1)1786; 80JCS(P1)2561, 80JCS(P1)2567], glycosylvinyl ketone (89LA247), or 1-acetyl-1-chloro-2-glycosylethene (75JOC2481) to give 3-glycosylpyrazoles **290** (Scheme 63).

3-Pyrazolyl C-nucleosides were formed according to the nucleoside-nucleoside transformation approach by cleavage of the pyrimidine ring of formycin N-6 oxide (**293**) or formycin B (**6**). Photohydrolytic [84JCS(P1)2421] or acid-catalyzed hydrolytic cleavage (76JHC1359; 82JA1073) of the former gave **292** and **294**, respectively, whereas hydrazinolysis of the latter gave the hydrazide **295**, which upon treatment with Raney nickel gave **296** (76JHC1359) (Scheme 64). Compound **296** was found inactive against L1210 leukemia cells in culture, which indicated that replacement of the pyrazole OH of pyrazofurin by an NH_2 culminated in loss of antileukemic activity (76JHC1359). This result supported Gutowski's proposal (75ANY544) that the 4OH of pyrazofurin is essential for its biological activity.

4-Deoxypyrazofurin (**302**) was prepared by the removal of the amino group **297** followed by mild hydrolysis of the cyano function of the resulting **299** [84JCS(P1)2367], by removal of the amino group of **300** followed by amidation of **301** (82CCC2004), or by 1,3-dipolar cycloaddition of methyl propiolate onto the β -D-ribofuranosyldiazomethane derivative **303** followed



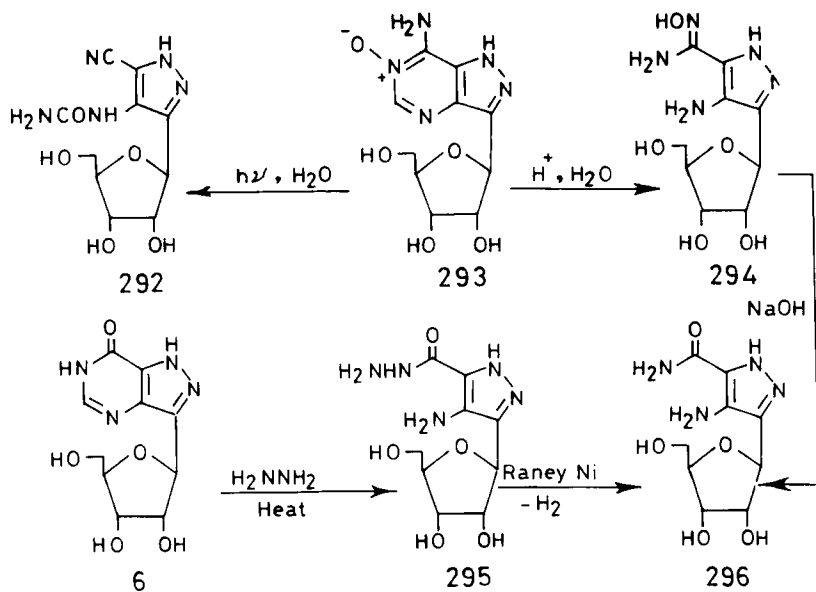
$\text{G}^1 = -\text{C}\equiv\text{CPh}, -\text{CH}_2\text{COOEt}, -\text{CH}\equiv\text{CHOAc}$

$\text{G}^2 = -\text{C}\equiv\text{CCHO}, -\text{C}\equiv\text{CCH}(\text{OEt})_2, -\text{CH}=\text{CClCOMe}$

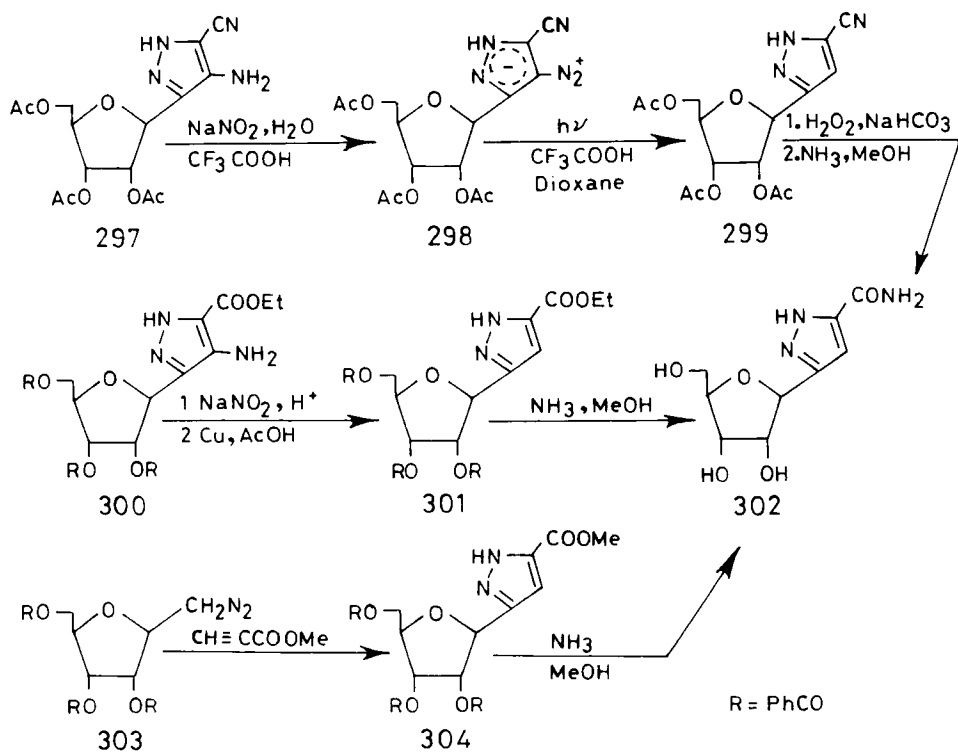
$\text{R} = \text{H}, \text{Ph}, \text{Me}$

$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Ac}, \text{PhCH}_2; \text{R}^1 + \text{R}^2 = \text{MeCMe}, \text{R}^3 = \text{Me}_3\text{CSiMe}_2$

SCHEME 63



SCHEME 64



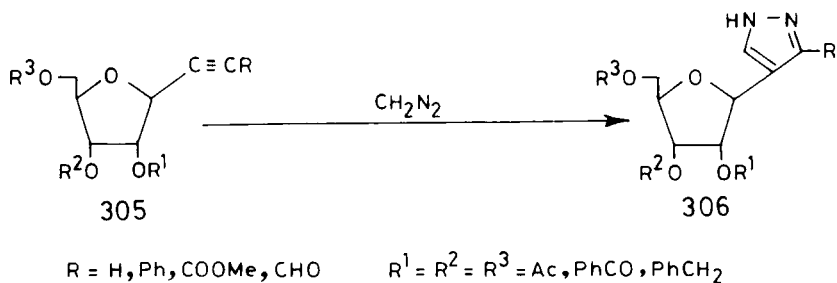
SCHEME 65

by ammonolysis of **304** (91S747) (Scheme 65). Compound **302** showed low virustatic activity (82CCC2004).

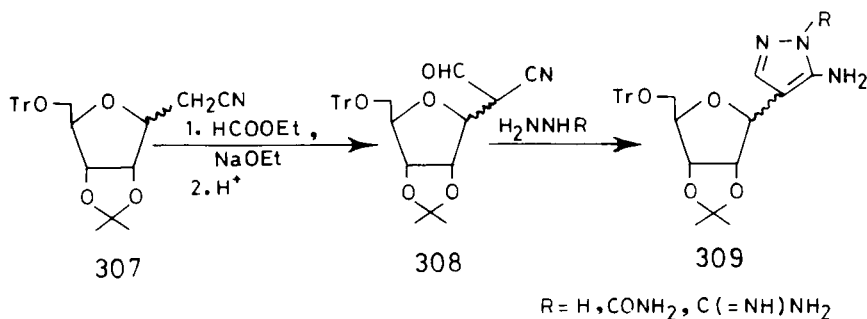
2. 4-Pyrazolyl C-Nucleosides

In cycloaddition of diazomethane to C-glycosylalkynes (**305**), the methylene group of the former usually acts as the more nucleophilic end of the 1,3-dipole, and the reaction therefore leads to the corresponding 4-glycosylpyrazoles **306** [71JHC525; 75JAP(K)75/59368; 75MI3; 76AQ987, 76JHC175, 76JOC84; 77MI5; 83MI6] (Scheme 66).

Cyclocondensation of hydrazines with 2-glycosylcyanoacetaldehyde (**308**) gave 4-glycosylpyrazoles (**309**) (76JHC175; 79JOC4547; 80JHC1435; 84H345, 84JHC389) (Scheme 67). Compounds **309** showed no inhibitory activity against P815 mouse leukemic cells (80JHC1435).



SCHEME 66



SCHEME 67

C. PYRAZOLE HOMO C-NUCLEOSIDES

1. 3(5)-Pyrazolyl Homo C-Nucleosides

Sato and Noyori published two syntheses for homopyrazofurin (**311**) (79H141; 83BCJ2700), the most recent of which used the C-glycosylpyruvic ester **181** (Section VI,C; Scheme 34), which reacted with ethyl hydrazinoacetate to give **310** followed by ammonolysis and deprotection to **311** (Scheme 68).

Condensation of the bicyclic α -keto ester **313** with ethyl hydrazinoacetate gave the corresponding hydrazone **314**, which gave the bishomopyrazofurin **316** after cyclization, separation, ammonolysis, and deprotection (76CJC2940) (Scheme 69).

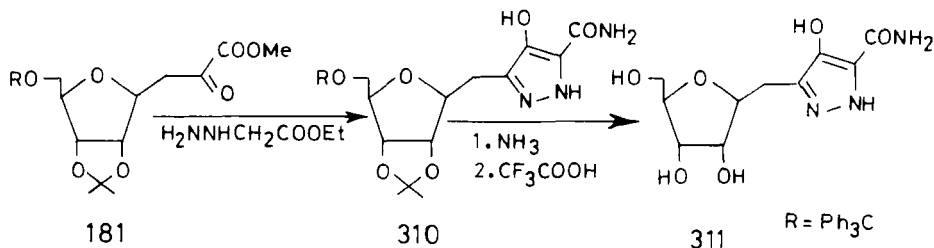
2. 4-Pyrazolyl Homo C-Nucleosides

Cycloaddition of diazomethane to the 4-(β -D-ribofuranosyl)but-2-enoate derivative **317** gave the pyrazol-4-yl homo C-nucleoside **318** (80BCJ1195) (Scheme 70).

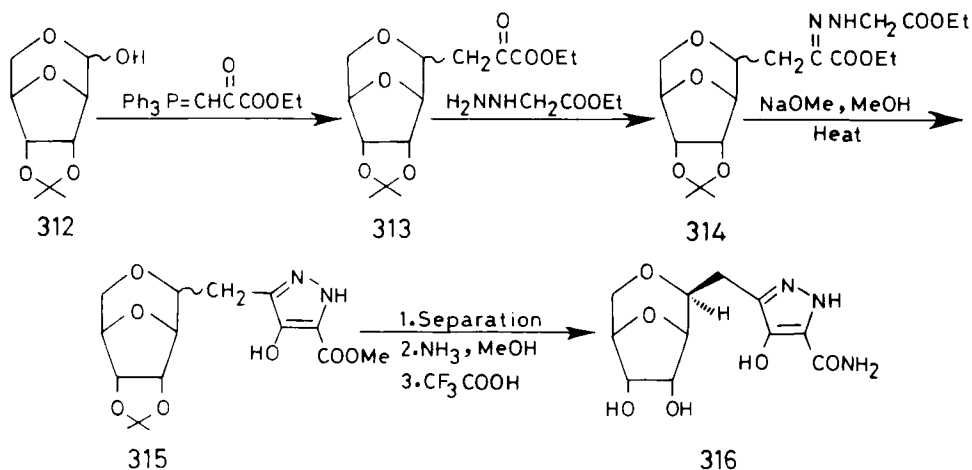
D. PYRAZOLE CARBOCYCLIC C-NUCLEOSIDES

1. 3(5)-Pyrazolyl Carbocyclic C-Nucleosides

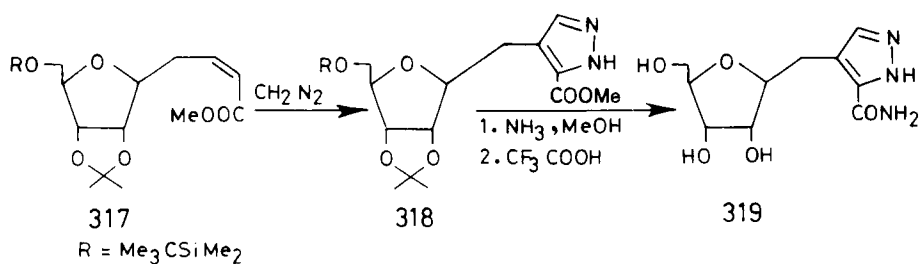
Carbocyclic pyrazofurin **322** was prepared from the carbocyclic α -keto ester **185** (Section VI, B; Scheme 35) and ethyl hydrazinoacetate as shown in Scheme 71 (76TL1063; 77CJC427). The 2'-deoxy analog of **322** was obtained from the 2'-deoxy analog of **185** by applying the same reactions as in Scheme 71 (76CJC2935). Carbocyclic pyrazofurin (**322**) was found inactive against bacteria, fungi, and viruses (76TL1063).



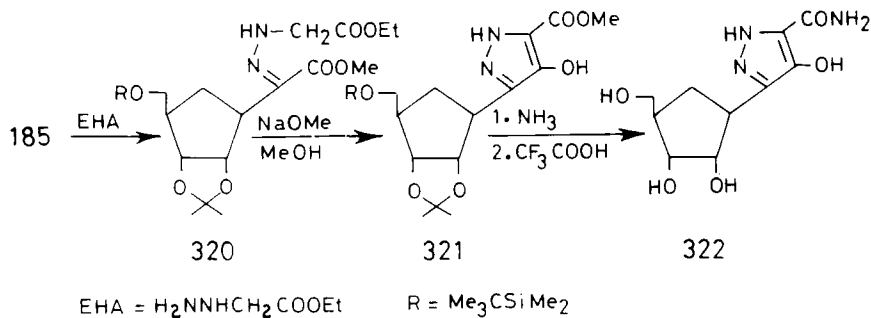
SCHEME 68



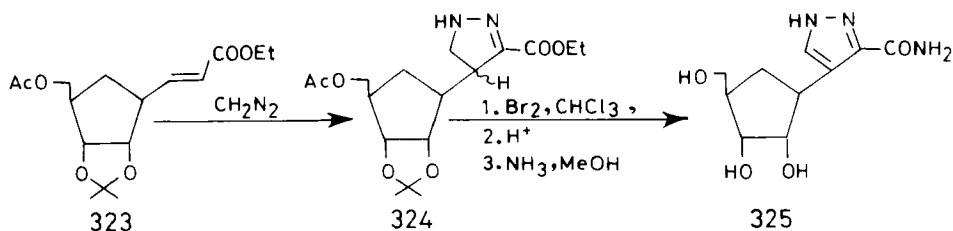
SCHEME 69



SCHEME 70



SCHEME 71



SCHEME 72

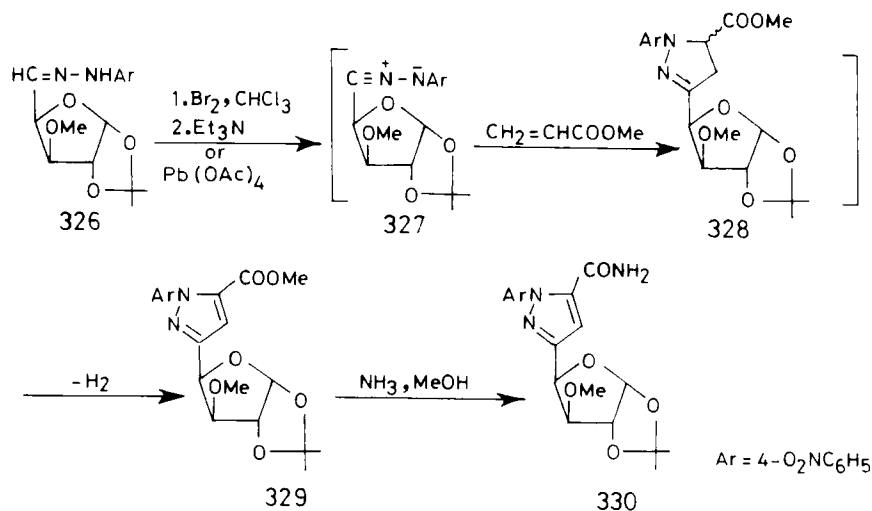
2. 4-Pyrazolyl Carbocyclic C-Nucleosides

Cycloaddition of diazomethane to the carbocyclic acrylic ester **323** gave the pyrazoline **324**, which was elaborated to **325** (76CJC861) (Scheme 72).

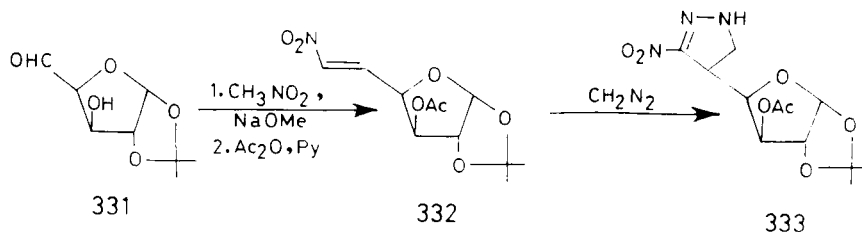
E. PYRAZOLE REVERSE C-NUCLEOSIDES

1. 3(5)-Pyrazolyl Reverse C-Nucleosides

Treatment of pentodialdofuranose 4-nitrophenylhydrazones (e.g., **326**) (93H833) or the corresponding hydrazoneyl bromides (71HCA921) with reactive alkenes (93H833) or alkynes (71HCA921) gave pyrazole reverse C-nucleosides (e.g., **329**) through 1,3-dipolar cycloaddition onto the nitrilimine intermediate **327** (93H833) (Scheme 73).



SCHEME 73



SCHEME 74

2. 4-Pyrazolyl Reverse C-Nucleosides

Cycloaddition of diazomethane onto the unsaturated nitro sugar derivative **332** gave **333** (87MI3) (Scheme 74).

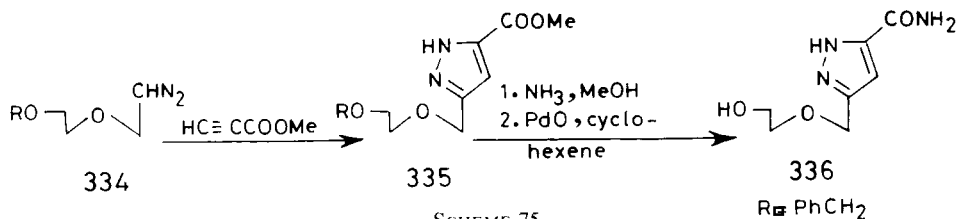
F. PYRAZOLE ACYCLO C-NUCLEOSIDES

1. 3(5)-Pyrazolyl Acyclo C-Nucleosides

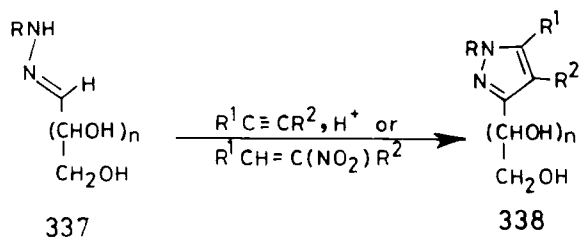
Like their cyclic analogs, 3-pyrazolyl acyclo C-nucleosides **336**, **338**, and **342** were prepared by 1,3-dipolar cycloaddition of alkenes or alkynes to acyclic sugar derivatives of diazoalkanes (e.g., **334**) (67CCC3787; 72MI6; 76AQ987; 90JOC5535) (Scheme 75), *aldehyde*-sugar arylhydrazones (**337**) [82MI12; 83AQ(C)152; 86AQ(C)204; 88MI10; 89MI10; 91AQ126, 91MI9] (Scheme 76), or *aldehyde*-sugar hydrazone halides (e.g., **339**) (69HCA2569; 70HCA1484; 71HCA921) (Scheme 77).

Cycloaddition of 1-(poly-*O*-acetylallditol-1-yl)-2-nitroethenes (**228**) to hydrazones of aromatic aldehydes afforded the corresponding 3-(poly-*O*-acetylallditol-1-yl)pyrazoles (**344**) (91MI7) (Scheme 78).

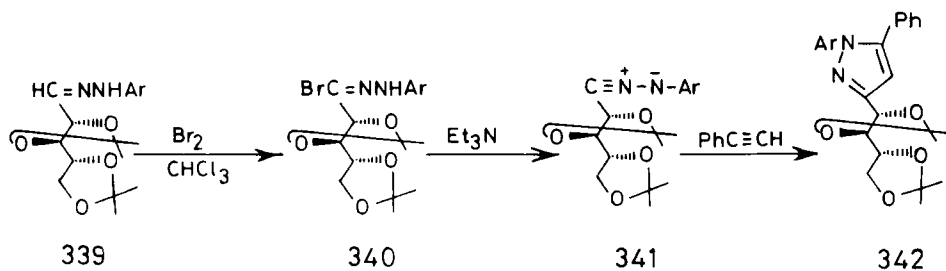
After Ohle reported his work on the base-catalyzed intramolecular rearrangement of dehydro-L-ascorbic acid phenylosazone (**345**) to 1-phenyl-4-phenyl-3-(1-*threo*-tritol-1-yl)pyrazolin-5-one (**347**) (34CB1750), many



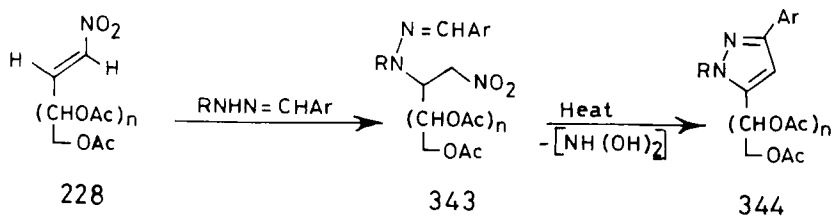
SCHEME 75



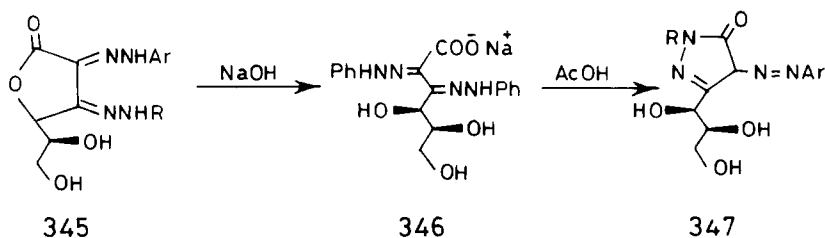
SCHEME 76



SCHEME 77



SCHEME 78

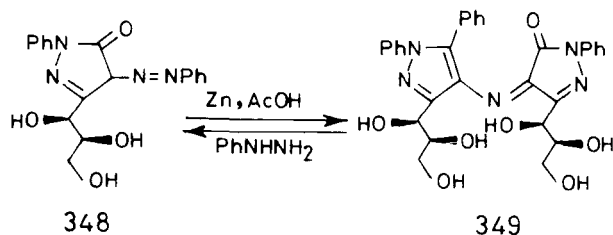


Ar = R = Ph, 4 - (Me, F, Cl, Br, or I) C₆H₄

Ar = 4 - (Me, Cl, Br, or I) C₆H₄; R = Ph

Ar = Ph; R = Me, 4 - (Me, Cl, Br, I, or NO₂) C₆H₄

SCHEME 79

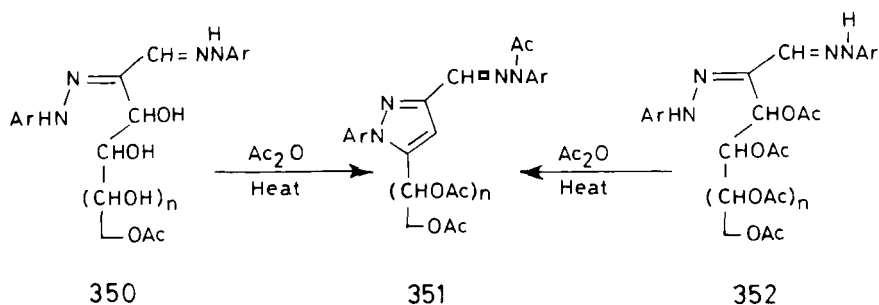


SCHEME 80

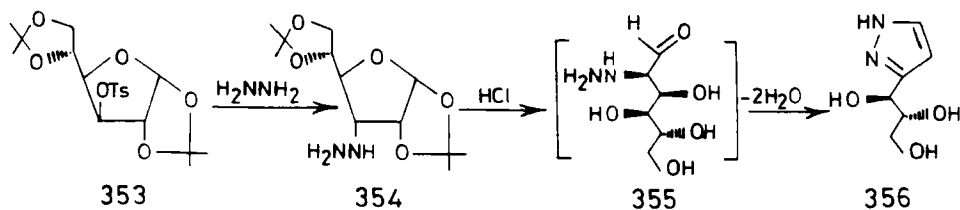
publications appeared describing the preparation of various analogs of **347** and derivatives thereof [68JCS(C)2248; 76CI(L)372, 76MI13; 77MI6, 77MI8, 77MI10; 78MI11; 79MI8, 79PHA531; 80MI6, 80MI7; 88MI11; 91MI1] (Scheme 79). Reduction of this type of pyrazole acyclo C-nucleosides (e.g., **348**) gave the bimolecular products **349** (72JOC3523; 91MI2) (Scheme 80).

Heating osazones of monosaccharides (**350**) [63JCS4929; 64JOC1565; 65MI5; 68JCS(C)2411, 68MI6] or reducing disaccharides (64JOC3072) with acetic anhydride, El Khadem and his group obtained the 3-(alditol-1-yl)pyrazoles (**351**) that were formed as a result of intramolecular cyclodehydration and simultaneous *N*- and *O*-acetylation. Compounds **351** were also obtained from poly-*O*-acetyl derivatives of osazones (**352**) by heating with acetic anhydride (72CB954; 76MI4; 85MI8, 86MI3), and a mechanism for their formation was suggested (76MI4; 85MI8) (Scheme 81).

Hydrazino [75JHC75; 85JCS(P1)1425], hydrazono (70CB1846; 92RTC427), or hydrazido groups (94T7219) located in a β position with respect to the sugar carbonyl (e.g., **355**) undergo facile intramolecular dehydrocyclization to 3-(alditol-1-yl)pyrazoles (**356**) (Scheme 82).



SCHEME 81



SCHEME 82

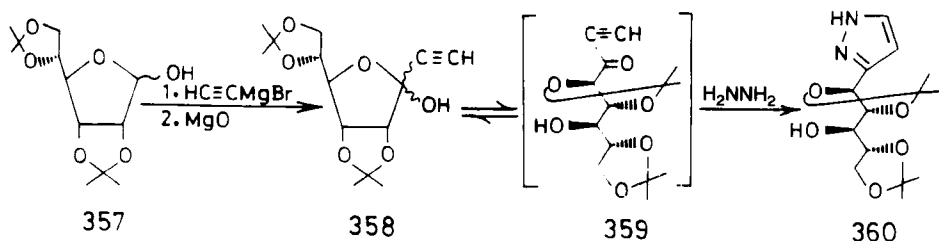
Aldonoylacetylenes (**358**) react with hydrazines to give the corresponding 3-(alditol-1-yl)pyrazoles (**360**) [77JCS(P1)1786; 80JCS(P1)2561; 81JCS(P1)2258] (Scheme 83).

Assembling the modified sugar moiety onto a pyrazole subunit (e.g., **361**) is the most commonly used route for the synthesis of acyclo *C*-nucleosides with truncated sugar moieties (**363**) [85JCS(P1)2087; 91MI10] (Scheme 84). Acyclopyrazofurins such as **363** were tested for their antiviral activities against a wide variety of viruses, but showed only slight inhibition of human cytomegalovirus (91MI10).

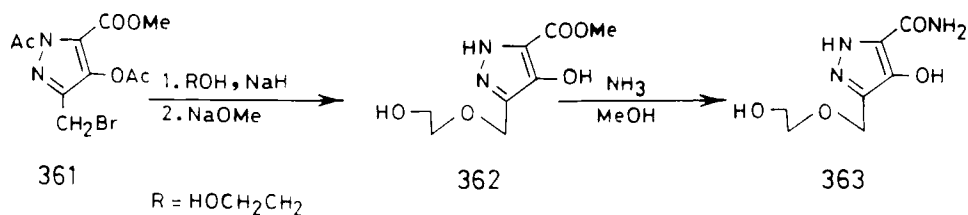
2. 4-Pyrazolyl Acyclo *C*-Nucleosides

Reaction of the enolic ether **366** of 3-(alditol-1-yl)-2-formylpropionitrile (**365**) with hydrazine gave the 4-alditolyl-2-aminopyrazole **367** (88JOC2413) (Scheme 85).

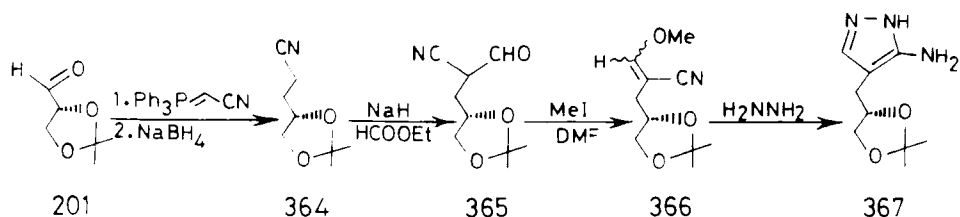
Cycloaddition of the 1-(poly-*O*-acetylallditol-1-yl)-2-nitroethenes **228** to diazoalkanes gave the corresponding 4-(poly-*O*-acetylallditol-1-yl)pyrazolines **368**, which undergo elimination of a molecule of nitrous acid forming the 4-pyrazolyl acyclo *C*-nucleosides **369** (88JOC5648; 91MI6, 91MI8; 94MI4) (Scheme 86).



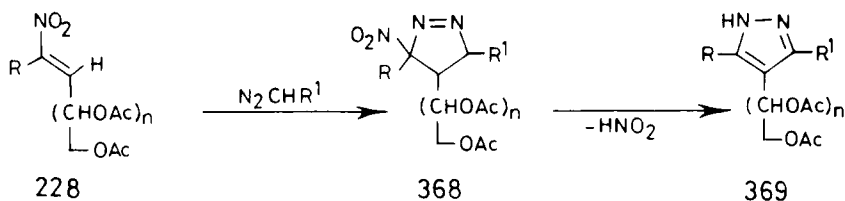
SCHEME 83



SCHEME 84



SCHEME 85



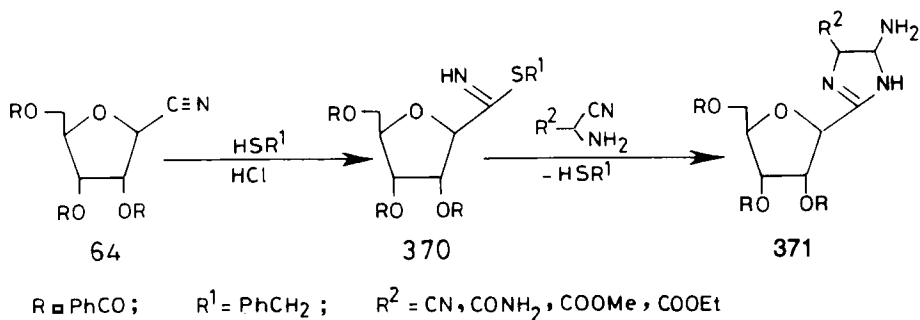
SCHEME 86

VIII. 1,3-Diazole C-Nucleosides

A. IMIDAZOLE C-NUCLEOSIDES

1. 2-Imidazolyl C-Nucleosides

Igolen and his group prepared the *O*-protected *C*-β-D-ribofuranosylthioformimidate **370** [71JCS(CC)1267; 72MI1; 75JHC111], *C*-2-deoxy-α, β-D-ribofuranosylthioformimidate (73TL2971; 75MI7, 75T2914), and *C*-β-D-arabinofuranosylthioformimidate (76MI3) and utilized them to synthesize the corresponding 2-imidazolyl *C*-nucleosides such as **371** by condensation with α-aminocyanoacetic acid derivatives (Scheme 87). *C*-Glycosylformimidates have also been used in place of the thioformimidates in this reaction [79JAP(K)79/100371; 80JOC203].



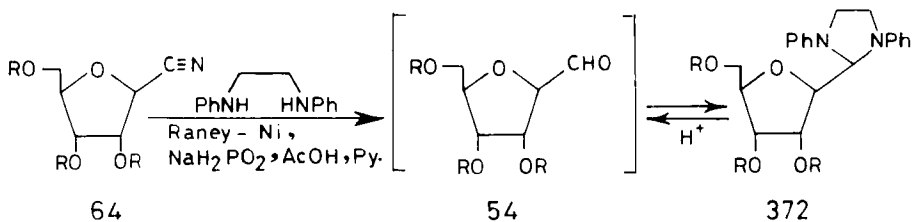
SCHEME 87

2-Glycosyl-1,3-diphenylimidazolidines (**372**) were prepared by reacting glycosyl cyanides (**64**) with 1,2-diphenylaminoethane. The diphenylimidazolidine ring of **372** is stable to alkali but is acid sensitive; it is actually used to mask the aldehyde function of **54** [73JOC1836, 73JOC1841; 79MI14; 88TL1841; 89HCA1825; 95MI1] (Scheme 88).

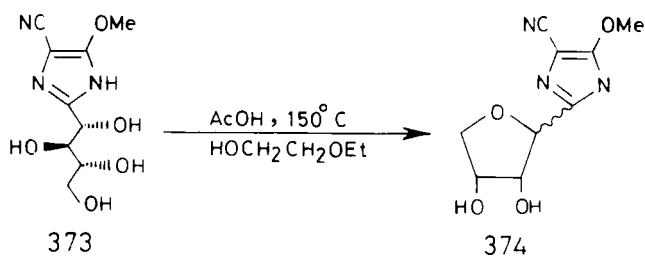
Acid-catalyzed cyclization of 2-(*ribo*-tetritol-1-yl)imidazole (**373**) (Section VIII,D,1) by heating with acetic acid gave a separable mixture of the 2-(α,β -D-erythrofuransyl)imidazole **374** [81JCS(CC)110] (Scheme 89).

2. 4(5)-Imidazolyl C-Nucleosides

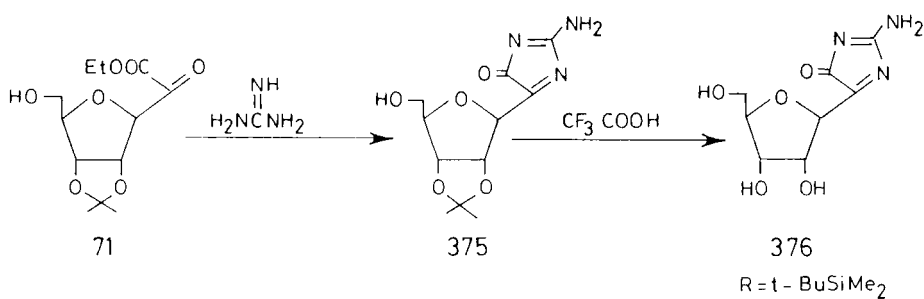
Reaction of the C- β -D-ribofuransylglyoxylic ester **71** with guanine gave the imidazole ring of the 4-imidazolyl C-nucleoside **375** [84JCS(P1)657] (Scheme 90). Condensation of the 6-(β -D-ribofuransyl)-6-hydroxypyranone derivative **377** with alkyl- or arylamidines afforded **381** (90H2225) (Scheme 91). Similar multistep syntheses that involved construction of the imidazole ring on the sugar subunit have also been described (91TL6485; 94SL489).



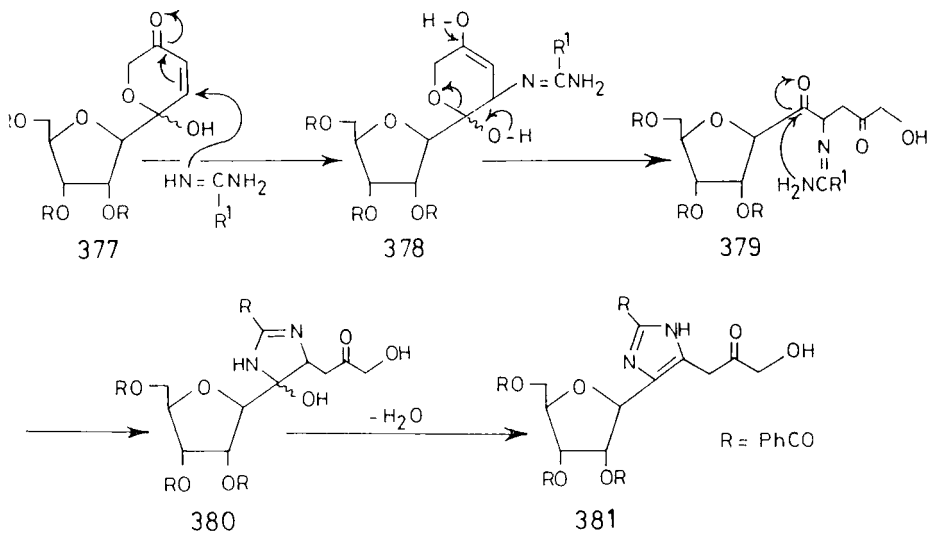
SCHEME 88



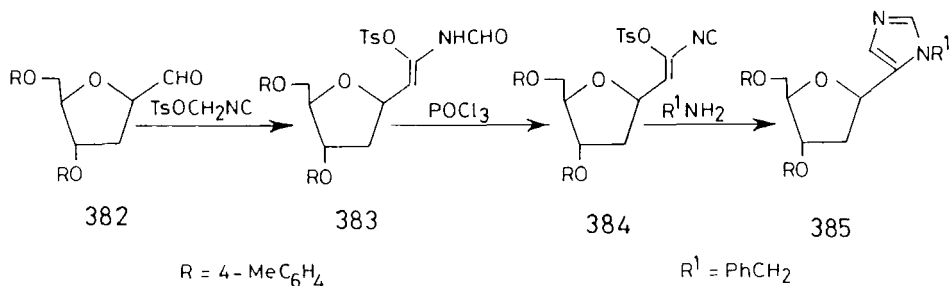
SCHEME 89



SCHEME 90



SCHEME 91



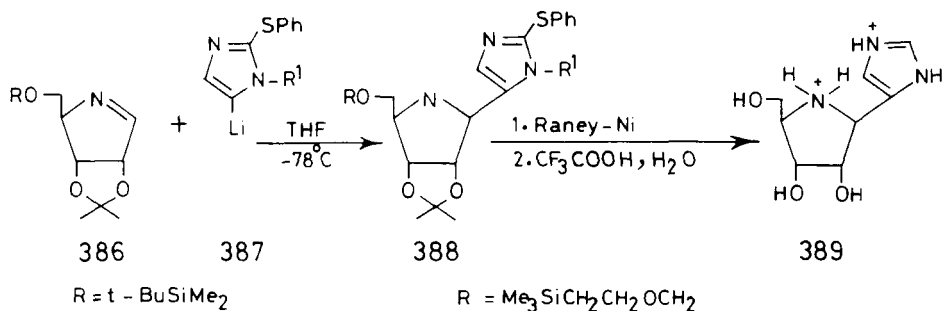
SCHEME 92

Building the imidazole ring of **385** was achieved by reaction of the 2-(glycofuranosyl)-2-isocyano-2-(4-tolylsulfonyloxy)ethene **384** with amines [95JCS(P1)3029] (Scheme 92).

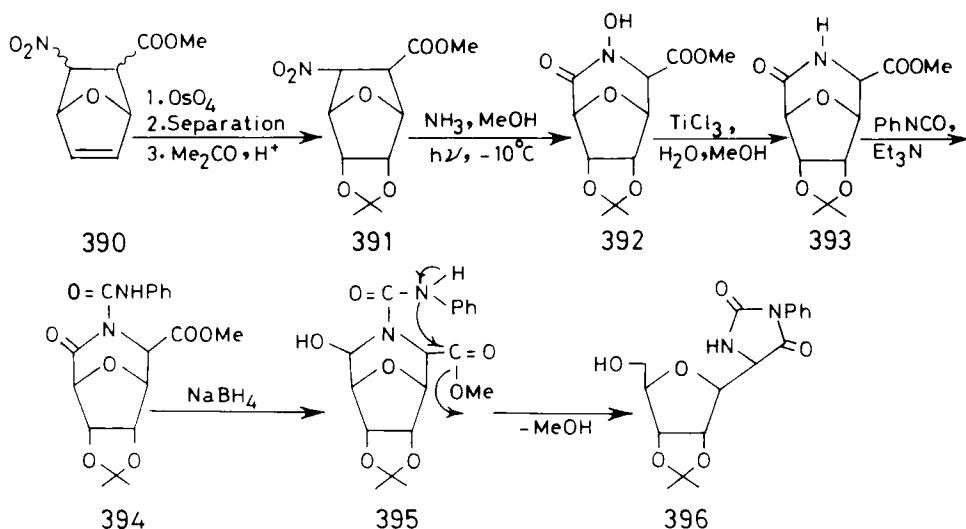
The imidazol-4-yl *C*-nucleoside analog **389** having a nitrogen-containing sugar moiety was obtained by direct condensation of its subunits **386** and **387** as shown in Scheme 93 (93TL7213). This analog (**389**) is a potent competitive inhibitor for nucleoside hydrolase from the trypanosome *Crithidia fasciculata* (93TL7213).

Only one total synthetic approach was reported for the synthesis of the 4-imidazolyl *C*-nucleoside **396** as depicted in Scheme 94 (90TL6547).

Compounds belonging to this category of *C*-nucleosides (**399**) were prepared by cyclization of the polyhydroxyalkyl chains of 4-(alditol-1-yl)imidazoles (**398**) (Section VIII,D,2) by heating their aqueous solutions under pressure (68AQ1013; 73AQ771; 77AQ1184) or by heating their solutions in dilute trifluoroacetic acid [77AQ1184; 78AQ336; 83AQ(C)345; 88MI6] or acetic acid [81JCS(CC)110; 94MI3]. Usually a separable mixture of the two anomeric *C*-nucleosides is formed in varying proportions that depend



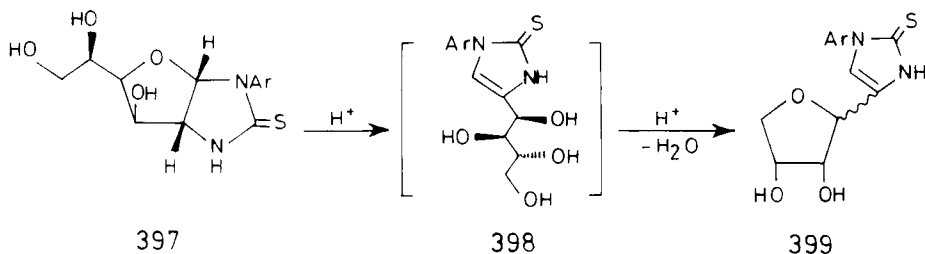
SCHEME 93



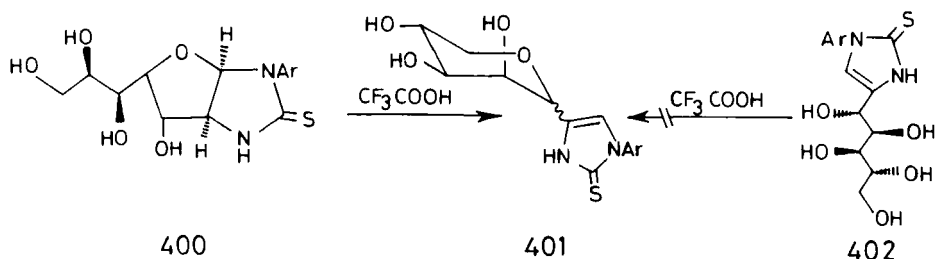
SCHEME 94

on the reaction conditions, the electronic effect of the substituents on the imidazole ring, and the configuration of the alditolyl chain. 1-Aryl-(1,2-dideoxyglycofurano)[2,1-*d*]imidazolidine-2-thiones (**397**), the precursors of **398**, also undergo acid-catalyzed isomerization and dehydration to the corresponding *C*-nucleosides **399** (76AQ79) (Scheme 95). X-ray crystallographic analysis confirmed the structure of some of these compounds (**399**) [75AX(B)468].

1-Aryl-4-(*D*-galacto-pentitol-1-yl)imidazoline-2-thiones **402** failed to undergo acid-catalyzed cyclization; the β -*D*-glycero-*L*-gluco-heptofurano [2,1-*d*]imidazoline-2-thiones precursor **400**, however, readily cyclized to a mixture of 4-(α , β -*D*-lyxopyranosyl)imidazoline-2-thione (**401**) (88MI9) (Scheme 96).



SCHEME 95



SCHEME 96

The partially *O*-benzylated imidazol-4-yl acyclo *C*-nucleoside **403** (Section VIII.D.2; Scheme 111) was cyclized with tetramethylazodicarboxamide to **404** (95TL3165) (Scheme 97).

B. IMIDAZOLE REVERSE C-NUCLEOSIDES

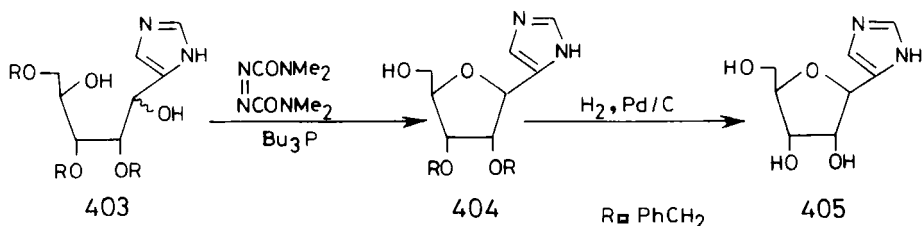
1. 2-Imidazolyl Reverse C-Nucleosides

Carbon-carbon bond formation between the hexodialdopyranose derivative **406** and 2-trimethylsilylimidazole gave the reverse *C*-nucleoside **407** (72ABC1445) (Scheme 98).

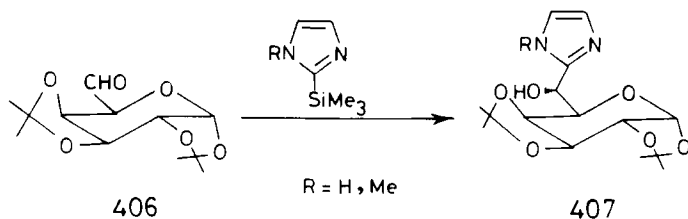
The 2-imidazolyl reverse *C*-nucleoside having an *N*-nucleoside head **409** was prepared by condensation of **408** with 1,2-diphenylaminoethane (79HCA2788) (Scheme 99).

C. THE NATURALLY OCCURRING IMIDAZOLE ACYCLO C-NUCLEOSIDE ANTIBIOTIC "CV-1"

This *C*-nucleoside antibiotic having a rather simple structure was isolated in 1987 by Yasuzawa *et al.* from a strain of *Streptomyces* sp. II, and its



SCHEME 97



SCHEME 98

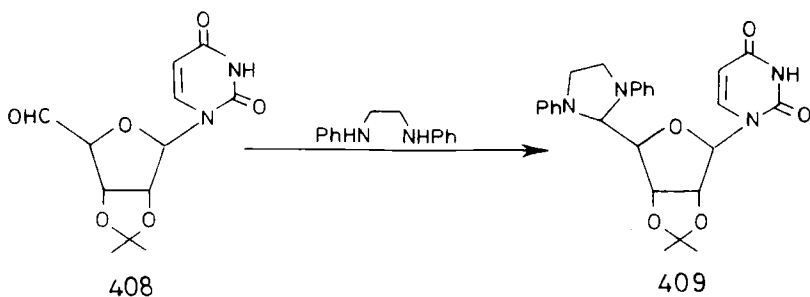
5-hydroxy-4-(D-*arabino*-tetritol-1-yl)imidazolidin-2-one structure (**15**) was determined by spectral as well as by chemical studies (87JAN727). This structure was further confirmed by synthesis from D-glucosamine hydrochloride (**210**) and ethoxycarbonyl isocyanate (87JAN727) (Scheme 100).

D. IMIDAZOLE ACYCLO C-NUCLEOSIDES

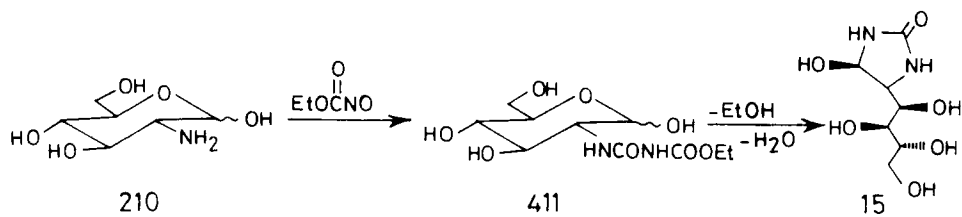
1. 2-Imidazolyl Acyclo C-Nucleosides

Oxidative cyclization of the ribopyranosylmaleonitrile adduct **412** afforded the 2-(D-*ribo*-tetritol-1-yl)imidazole **414** [81JCS(CC)110]. The reaction was suggested to take place through the imino(ribopyranosylimino) succinonitrile intermediate **413**, which formed an imidate ester that cyclized to **414**. The reaction mechanism, however, has not been studied (Scheme 101).

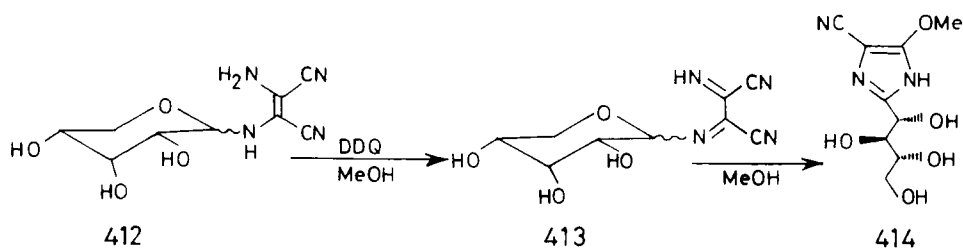
The truncated-sugar 2-imidazolyl C-nucleoside **417** was synthesized from the benzylthioimide **415** and aminocyanoacetamide (83JHC1169) (Scheme 102), whereas a mixture of the two diastereoisomers of **419** was obtained by direct condensation of the two subunits (72ABC1443; 94H673; 95TL1085) (Scheme 103).



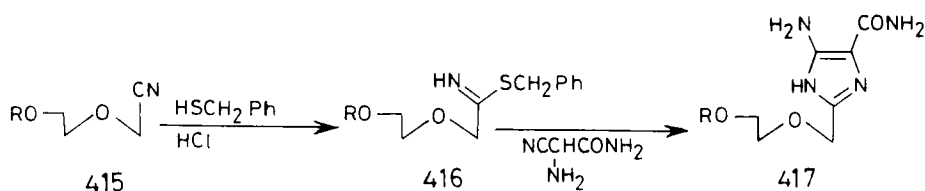
SCHEME 99



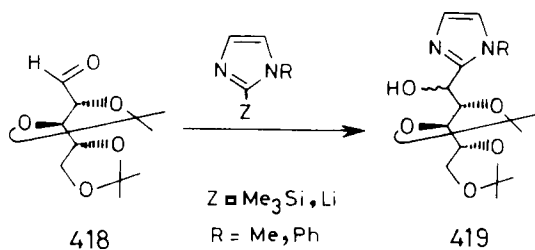
SCHEME 100



SCHEME 101



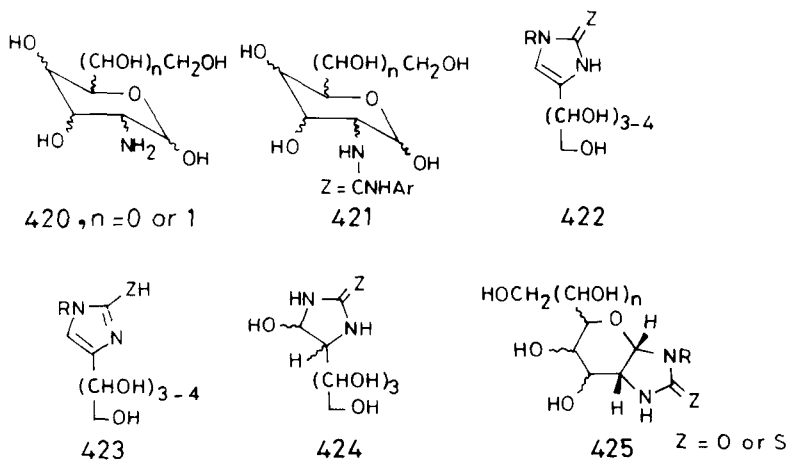
SCHEME 102



SCHEME 103

2. 4(5)-Imidazolyl Acyclo C-Nucleosides

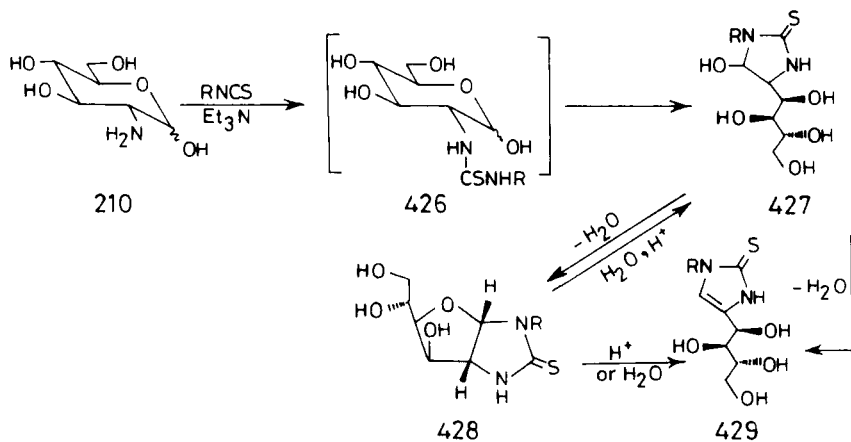
Reaction of 1-amino-1-deoxyketose or 2-amino-2-deoxyaldose monosaccharides with alkali metal cyanates or thiocyanates and with alkyl or aryl isocyanates or isothiocyanates is one of the most extensively used and intensively studied routes to prepare these compounds (76MI5). Various structures were assigned to the reaction products obtained from 2-amino-2-deoxyaldoses (**420**), among which are the 2-ureido-2-deoxyaldopyranoses **421** [10MI1; 66LA(696)214; 70MI12; 88AQ(C)5], the 4-(alditol-1-yl)imidazolin-2-ones and their thiones **422** [01CB3840; 03CB618; 22ZPC170; 28YZ584; 48AQ(B)233; 49AQ(B)1527; 53CB1453; 57HCA342; 60HCA713; 63T1883; 72MI7; 95PJC90], the 4-(alditol-1-yl)-2-hydroxy-2-mercaptoimidazole (**423**) [01APC223; 02ZPC353; 62BJ(82)43P], the 4-(alditol-1-yl)-5-hydroxy-imidazolin-2-thiones **424** [64BJ(92)57P; 91MI5], and the cis-fused glycopyrano[2,1-*d*]imidazolidin-2-ones and their thiones (**425**) [56CB1246; 58CB668; 61AQ(B)379, 61HCA403; 63LA(669)146, 63T1883; 64AQ(B)653; 65NEP6507269, 65NEP6507271, 65NEP6507423; 66AQ(B)999; 68AQ407; 75OPP291).



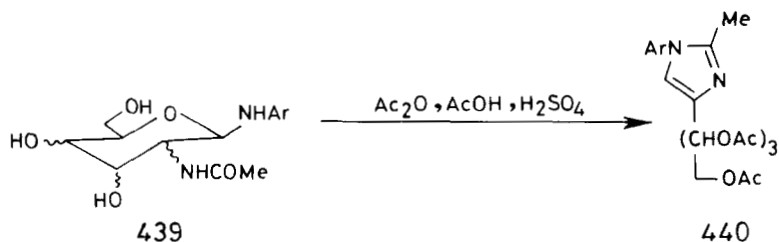
Although quantitative periodate oxidation results obtained by Garcia Gonzalez [51AQ(B)299] did not reconcile with the 4-(alditol-1-yl)imidazole structure **423** that was assigned to some of the products, Fritz *et al.* rejected the glycopyrano[2,1-*d*]imidazolidine structure **425** and proved by ¹HNMR studies that they possess glycofurano[2,1-*d*]imidazolidine structures such as **428** (68HCA569) (Scheme 104). Later, Scott withdrew the 4-(alditol-1-yl)-2-mercaptoimidazole structure **423** he previously assigned [62BJ(82)43P] to the reaction product of glucosamine (**210**) with

phenyl isothiocyanate and found that the thioureido derivative **426** is the initial reaction product. Compound **426** is reactive and cyclizes to the 5-hydroxyimidazolidin-2-thione derivative **427**, which is capable of dehydration to the imidazolin-2-thiones **429** or cyclodehydrate to the glucofurano[2,1-*d*]imidazolidin-2-thione **428** (70MI12) (Scheme 104). The structure of **428** was confirmed by three-dimensional X-ray analysis [74AX(B)1801], and its isomerization to **429** in neutral or acid media was studied (84MI3; 88MI13). The corresponding oxo analogs of **428** and **429** were similarly obtained from the reaction of glucosamine with potassium cyanate (90MI4). Avalos *et al.* thoroughly studied the conditions under which the different products of the reaction are formed and found that (i) in neutral or basic media ($\text{pH} > 6$), the initially formed ureido derivatives (**421**) cyclize to 5-hydroxy-4-(alditol-1-yl)imidazolidines (**424**); (ii) in acid media ($\text{pH} < 6$) both the ureido (**421**) and the 5-hydroxyimidazolidine (**424**) derivatives are transformed to the cis-fused glycofurano[2,1-*d*]imidazolidine derivatives **433** through the protonated intermediates **431** and **432**; and (iii) in acid media, the 5-hydroxyimidazolidine **424** also dehydrates to imidazoline derivatives **422** according to the mechanism shown in Scheme 105 (93T2655, 93T2676; 94T3273).

1-Amino- or 1-substituted amino-1-deoxyketoses (**434**) also react with cyanate (60HCA1787; 76AQ991) and thiocyanate anions [60HCA1787; 84AQ(C)102] and alkyl or aryl isothiocyanates [73MI4; 85AQ(C)147, 85MI7] to afford the corresponding 4-(alditol-1-yl)imidazoline derivatives **435**. 4-(Alditol-1-yl)imidazoles (**436**) were obtained from the corresponding imidazoline-5-thiones (**435**; $\text{Z} = \text{S}$, $\text{R}^1 = \text{H}$) by desulfurization with oxygen



SCHEME 104



SCHEME 107

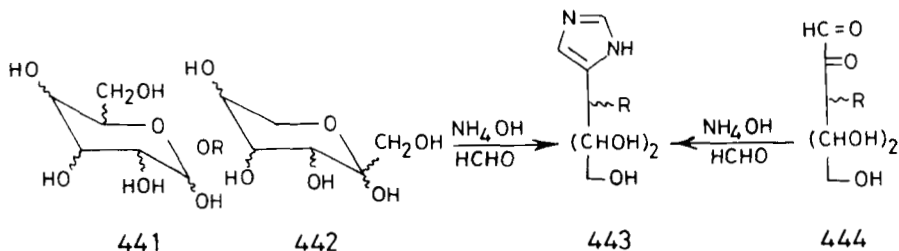
Acetolysis of 2-acetamido-2-deoxy- β -D-glycopyranosylamines (**439**) gave the corresponding 4-(poly-O-acetylalditol-1-yl)-2-methylimidazoles **440** (75MI6; 77MI9) (Scheme 107).

Treatment of aldohexoses (**441**) (31CR1136; 62MI2, 62MI3; 67ABC185; 68AJC505) or ketohexoses (**442**) (31CR1136; 73MI3) with ammonia gave many products, among which were 4-(alditol-1-yl)imidazoles (**443**, $\text{R} = \text{OH}$), 4-(2-deoxyalditol-1-yl)imidazoles (**443**, $\text{R} = \text{H}$). Formation of these compounds was proved to take place as a result of alkaline degradation of the monosaccharides to the corresponding hexosuloses (glycosones) (**444**, $\text{R} = \text{OH}$), 3-deoxyhexosuloses (**444**, $\text{R} = \text{H}$), and formaldehyde (31CR1136; 68AJC505) (Scheme 108). Heating sucrose with urea also gave many products from which 4-(D-arabino-tetritol-1-yl)imidazolidin-2-one was isolated (67MI2).

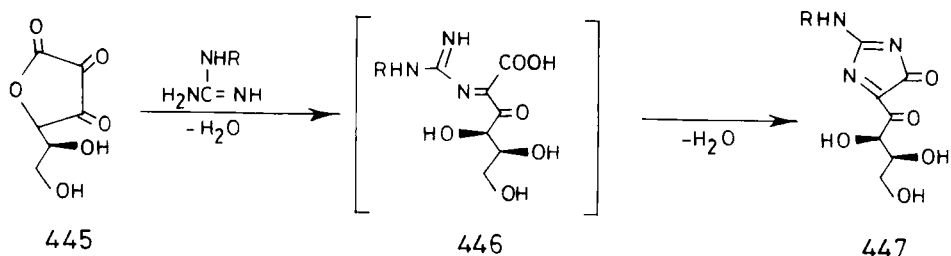
Condensation of dehydro-L-ascorbic acid (**445**) with guanidine or substituted guanidines gave **447** (92T6385) (Scheme 109).

Reaction of the D-gluconoylhydrazine derivative **448** with methyl glycinate gave **449**, which cyclized with alkali to the 4-(alditol-1-yl)imidazolidine-2,5-dione **450** [73ACH(75)185] (Scheme 110).

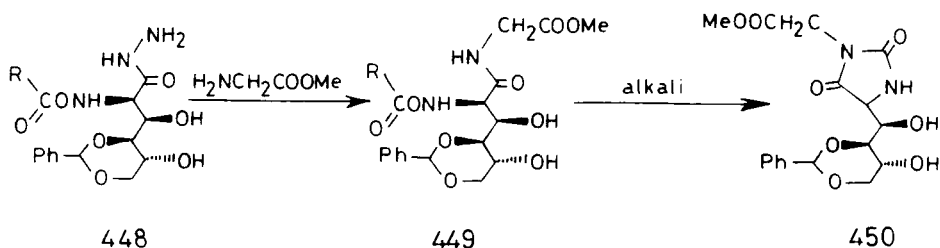
Synthesis of the imidazol-4-yl acyclo C-nucleoside **403** has been described (93MI2; 95TL3165) by condensation of the aldehydo-sugar derivative **51** with 4-lithioimidazole to give the hemiacetal C-nucleoside **451**, which formed **403** upon treatment with an acid (Scheme 111).



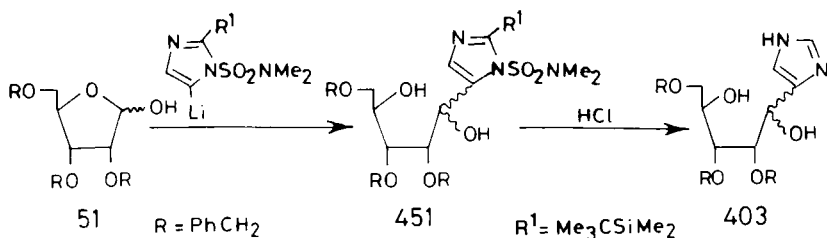
SCHEME 108



SCHEME 109



SCHEME 110



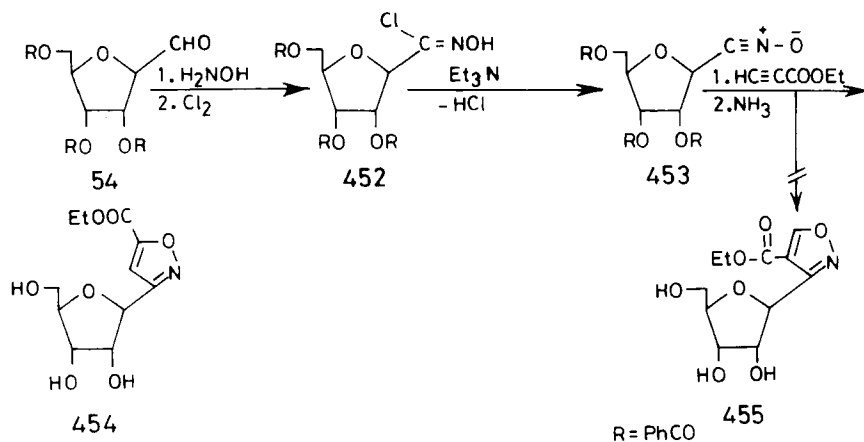
SCHEME 111

IX. 1,2-Oxazole C-Nucleosides

A. ISOXAZOLE C-NUCLEOSIDES

1. 3-Isoxazolyl C-Nucleosides

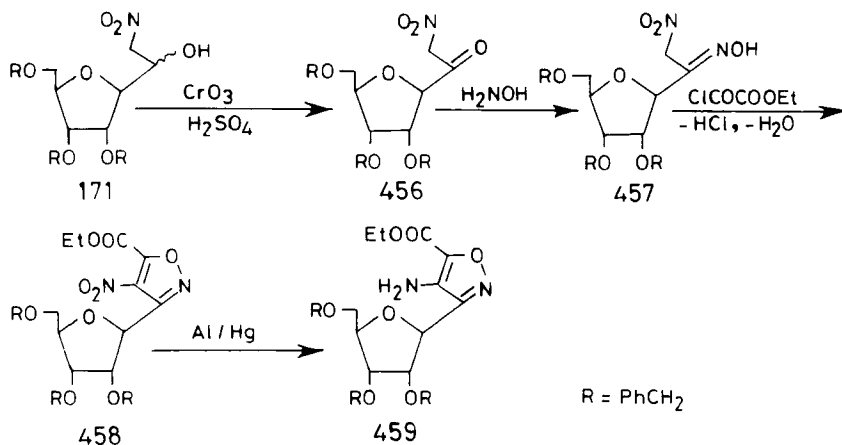
1,3-Dipolar cycloaddition of alkenes or alkynes to C-glycosynitrile oxides (**453**) (71HCA921; 75JOC2143; 83JOC1139) as well as to glycosyl silyl- and alkynitronates (88MI4, 88MI5), produced the corresponding 3-isoxazolyl



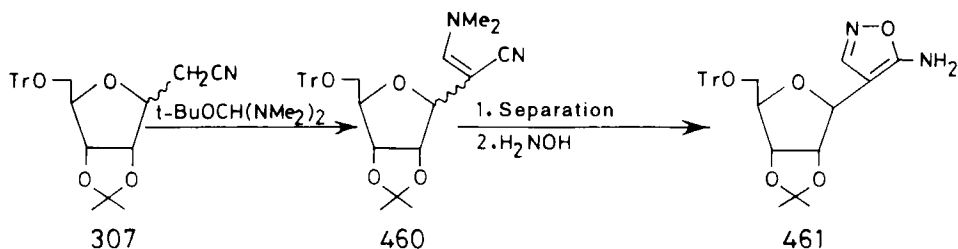
SCHEME 112

C-nucleosides **454** (Scheme 112). Evidently, this cycloaddition is regioselective because the alternative mode of addition leading to isomer **455** did not take place.

Cyclocondensation of the oxime **457** of 2,5-anhydro-D-allonoylnitromethane (**456**) with ethyl chlorooxacetate gave **459** (80TL3613; 91MI20) (Scheme 113).



SCHEME 113



SCHEME 114

2. 4-Isoxazolyl C-Nucleosides

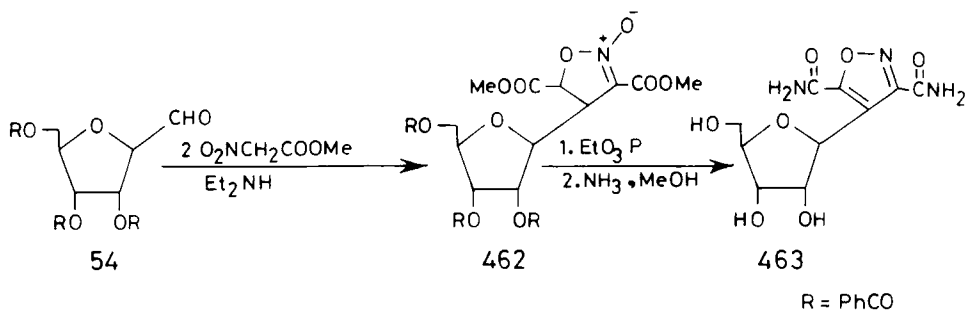
Reaction of the *C*-β-D-ribofuranosylacetonitrile **307** with *tert*-butoxybis(dimethylamino)methane gave a mixture of the α,β-anomers of **460**, which cyclized, after separation, with hydroxylamine to **461** (77JOC109; 78USP4096321) (Scheme 114).

Examples of this type of *C*-nucleosides (**462**) were prepared by one-step cyclization of *aldehydo*-sugar derivatives such as **54** with two equivalents of methyl nitroacetate (79BCJ2928) (Scheme 115).

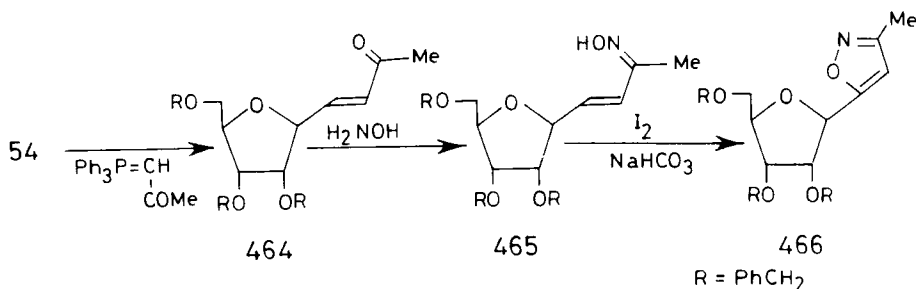
3. 5-Isoxazolyl C-Nucleosides

Oxidative cyclization of the oxime **465** derived from the *trans*-1-(β-D-ribofuranosyl)-2-acetylene **464** gave the 5-β-D-ribofuranosylisoxazole **466** (75JOC2143) (Scheme 116).

2-Acetoxyvinyl-α-D-lyxopyranosylketone (**467**) (89LA247) or enaminoglycosides (93H1617) cyclize upon reaction with hydroxylamine to 5-glycosylisoxazoles (**468**) (Scheme 117).



SCHEME 115



SCHEME 116

B. ISOXAZOLE CARBOCYCLIC C-NUCLEOSIDES

1. 5-Isoxazolyl Carbocyclic C-Nucleosides

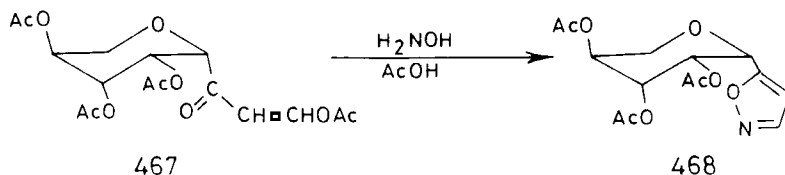
The only reported example of this kind is the 5-isoxalyl carbocyclic isoxazole **471** that was prepared by 1,3-dipolar cycloaddition of aryl nitrile *N*-oxides with the alkene side chain of **469** (76CJC861) (Scheme 118).

C. ISOXAZOLE REVERSE C-NUCLEOSIDES

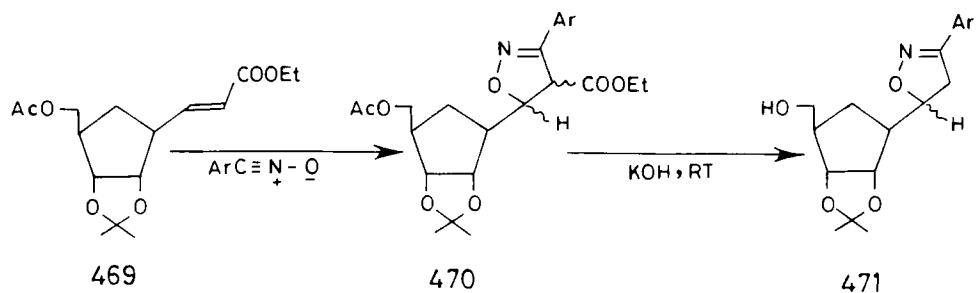
1. 3-Isoxazolyl Reverse C-Nucleosides

Cyclization of the hydroxamic acid halides **473** derived from pentodialdo-furanose oximes (**472**) with ethynylmagnesium halides gave the 3-isoxazolyl reverse C-nucleosides **474** (69HCA2569). The reaction has also been accomplished through transformation of the hydroxamic acid halides to the sugar nitrile *N*-oxides **475** followed by cycloaddition to alkynes to give **467** (70HCA1484; 71HCA921; 73MI6; 76MI8) (Scheme 119).

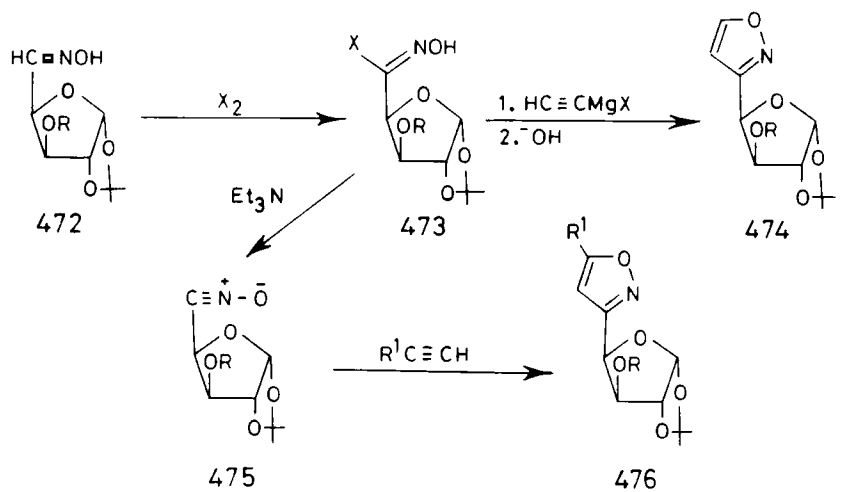
The 3-isoxazolyl reverse C-nucleosides **479** were obtained by the two routes depicted in Scheme 120, namely, (i) cyclocondensation of the 6-bromo-6-cyclohex-5-enofuranose derivative **478** with hydroxylamine and



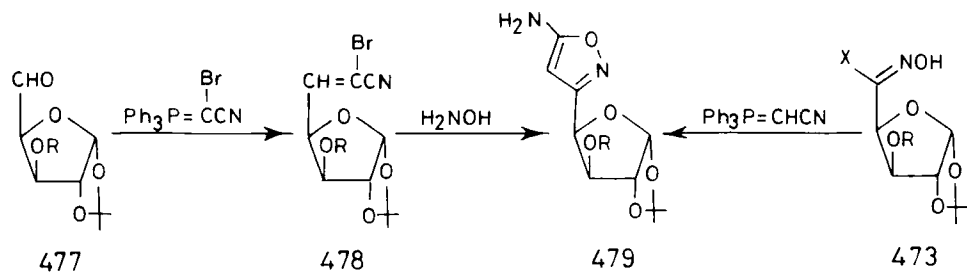
SCHEME 117



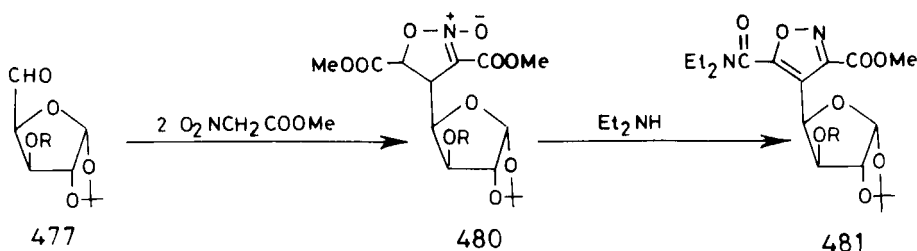
SCHEME 118

 $\text{R} = \text{Me}, \text{PhCH}_2$ $\text{R}^1 = \text{Ph}, \text{COOMe}, p\text{-O}_2\text{NC}_6\text{H}_4$ $\text{X} = \text{Cl}, \text{Br}$

SCHEME 119



SCHEME 120



SCHEME 121

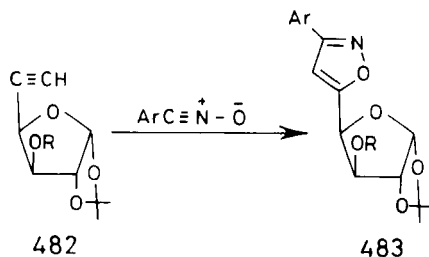
(ii) reaction of the hydroxamic acid halide **473** with cyanomethylidene triphenylphosphorane (75HCA1735).

2. 4-Isoxazolyl Reverse C-Nucleosides

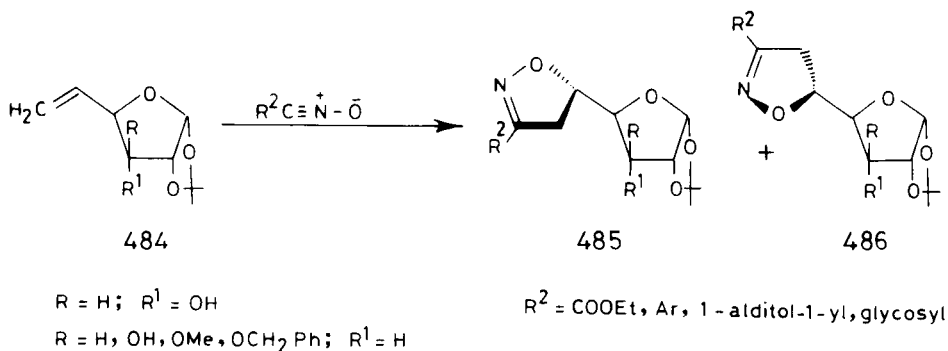
Reaction of two equivalents of methyl nitroacetate with the pentodialdofuranose sugar derivative **477** gave the 4-isoxazolinyln *N*-oxide derivative **480**, which underwent dehydration and monoamidation with diethylamine to give **481** (79BCJ2928) (Scheme 121).

3. 5-Isoxazolyl Reverse C-Nucleosides

1,3-Dipolar cycloaddition of aryl nitrite oxides to hex-5-ynofuranoses (**482**) afforded the 5-glycosylisoxazoles **483** (74HCA1505) (Scheme 122). Cycloaddition of the terminal olefinic sugars **484** to aryl nitrile oxides (70HCA1484; 89JOC793; 91JCS(CC)132, 91MI11, 91MI13; 94MI7), alditol nitrile oxides (93TL2831), or pentopyranosyl nitrile oxides [94JC-S(CC)993] was found to afford regiospecifically 1-substituted-5-glycosylisoxazolines **485** and **486**. The II-facial selectivity of the addition, however, differs with the configuration of the olefinic sugar moiety (**484**), and mix-



SCHEME 122



SCHEME 123

tures of varying proportions of the *anti*- and *syn*-5-glycosylisoxazoline isomers **485** and **486** were obtained. Their stereochemical structures were confirmed by X-ray analysis (Scheme 123).

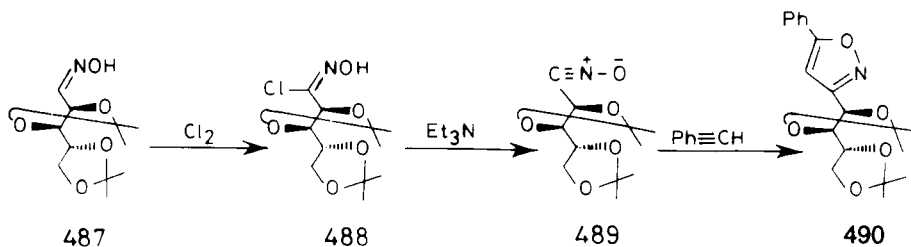
D. ISOXAZOLE ACYCLO C-NUCLEOSIDES

1. 3-Isioxazolyl Acyclo C-Nucleosides

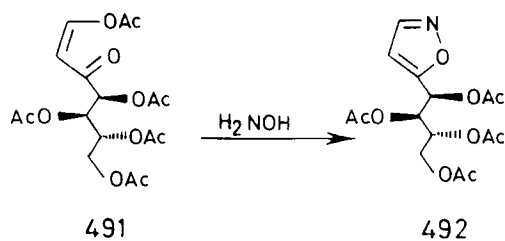
Alditolnitrile oxides such as **489** added to alkynes to give the 3-(alditol-1-yl)isoxazoles **490** (71HCA921) (Scheme 124). Using alkenes instead of alkynes gave 3-(alditol-1-yl)isoxazolines (94AGE1295).

The unsubstituted 3-(alditol-1-yl)isoxazole **492** was synthesized in one-step by reacting the 2-aldonoylvinyl acetate **491** with hydroxylamine (89LA247) (Scheme 125).

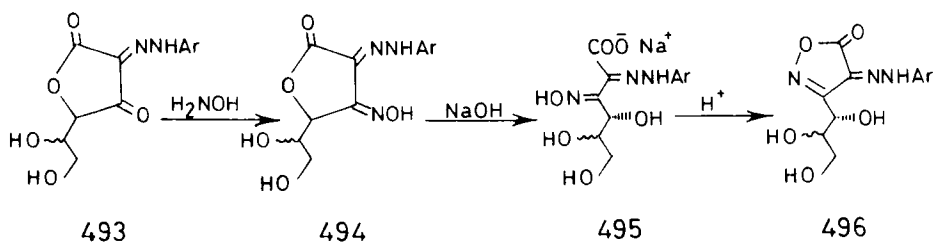
Molecular rearrangement of dehydro-D,L-ascorbic acid 2-arylhydrazones-3-oximes **494** by treatment with an alkali followed by acidification gave **496** [82MI13; 83MI8; 88MI3] (Scheme 126).



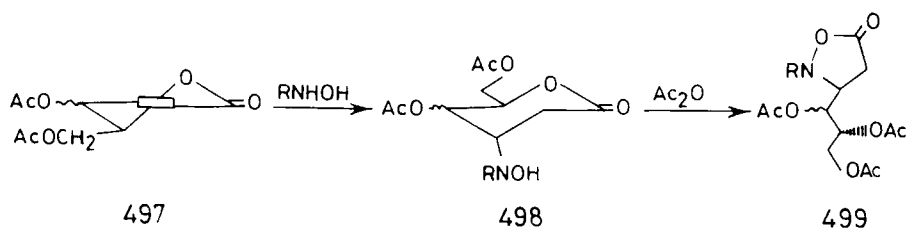
SCHEME 124



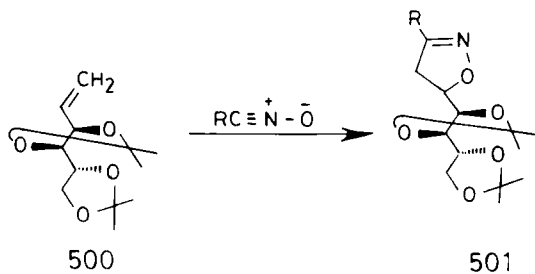
SCHEME 125



SCHEME 126



SCHEME 127



SCHEME 128

Addition of hydroxylamines on the double bond of the unsaturated aldonic acid lactones **497** gave the isoxazolidin-3-yl acyclo *C*-nucleosides **499** (92T10363) (Scheme 127).

2. 4-Isoxazolyl Acyclo *C*-Nucleosides

The previously mentioned reaction of *aldehydo*-sugars with two equivalents of methyl nitroacetate to prepare 4-isoxazolyl *C*-nucleosides (**463**) (Section IX,A,2) and the reverse analog **481** (Section IX,C,2) has also been used for the preparation of this type of analog from acyclo *aldehydo*-sugars (79BCJ2928).

3. 5-Isoxazolyl Acyclo *C*-Nucleosides

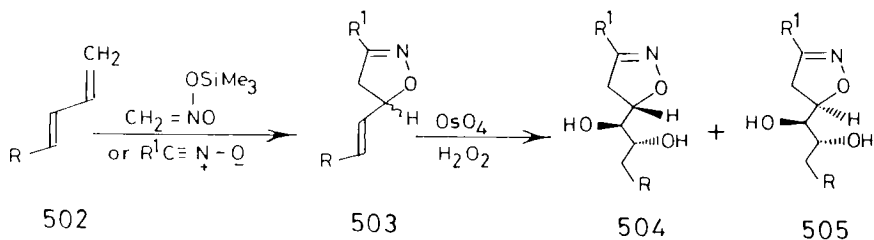
Addition of aryl nitrile oxides to alditolylalkenes (**500**) gave the corresponding 5-(alditol-1-yl)isoxazolines **501** (70HCA1484; 73HCA1303) (Scheme 128). Regioselective addition of silylnitronates or nitrile oxide to diolefines (**502**) gave isoxazolines with a double bond-containing side chain (**503**). *Cis*-dihydroxylation of the latter gave the diastereoisomeric 5-(alditol-1-yl)isoxazolines **504** and **505** (85T5569) (Scheme 129).

X. 1,3-Oxazole *C*-Nucleosides

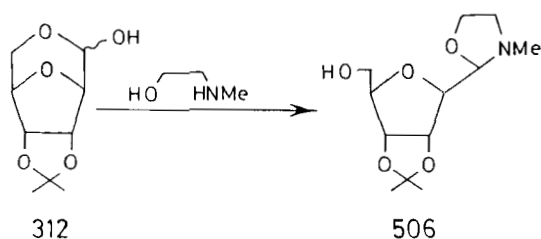
A. OXAZOLE *C*-NUCLEOSIDES

1. Oxazolyl *C*-Nucleosides

Only 2-oxazolyl *C*-nucleosides have been prepared; 4-oxazolyl and 5-oxazolyl *C*-nucleosides remain to be synthesized. The first compound of this type, **506**, was obtained by cyclocondensation of the bicyclic hemiacetal **312** with 2-(methylamino)ethanol (75CJC131) (Scheme 130).



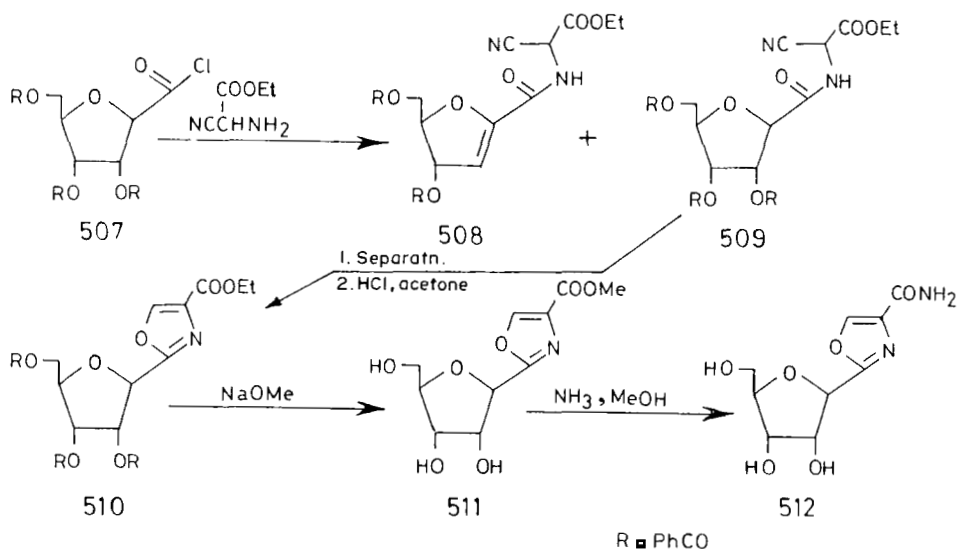
SCHEME 129



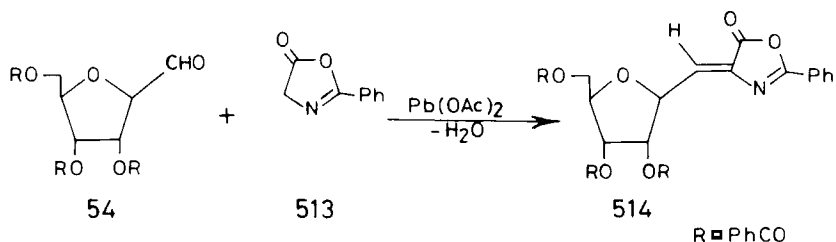
SCHEME 130

4-Carboxamido-2- β -D-ribofuranosyloxazole (oxazofurin) (**512**), the oxygen analog of the two synthetic C-nucleoside antitumor agents tiazofurin (**575**) and selenazofurin (**576**) (Section XII,A,1), was synthesized from the 2,5-anhydro-D-allonoyl chloride derivative **507** and ethyl 2-amino-2-cyanoacetate (90JMC2849) (Scheme 131). A similar synthesis by rhodium-catalyzed reaction of the nitrile of **507** with ethyl 2-formyldiazoacetate has been reported (93MI11).

Oxazofurin (**512**) was weakly cytotoxic toward B16 murine melanoma cells in culture, but inactive against P388 and L1210 murine leukemia and HL60 human leukemia (90JMC2849). It was also inactive against DNA



SCHEME 131



SCHEME 132

and RNA viruses, including HIV-1 (93MI11). Crystallographic and computational studies suggested that the marked differences in biological activity between oxazofurin and its thiazole and selenazole analogs are due to differences in electronic properties of the heterocycles or variation in C-glycosidic conformation resulting from the alteration in the charge distribution of these heterocycles (94JMC1684).

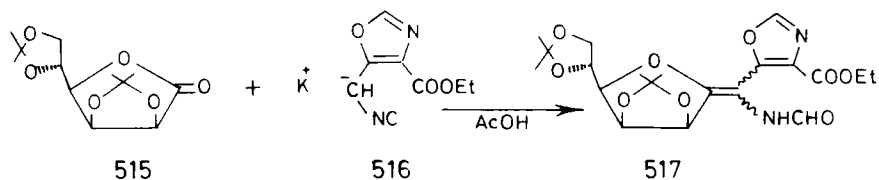
B. OXAZOLE HOMO C-NUCLEOSIDES

1. 4-Oxazolyl Homo C-Nucleosides

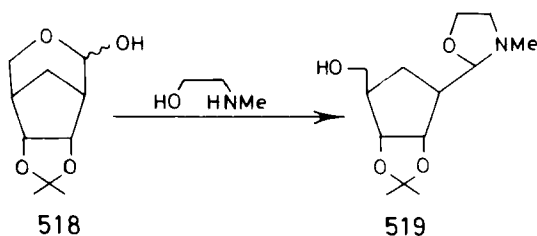
Reaction of the 2,5-anhydroallose derivative **54** with 2-phenyloxazolin-5-one (**513**) in the presence of lead tetraacetate gave the (*Z*)-4-hexofuranose-1-ylidene-5-oxazolone **514** (76MI11) (Scheme 132).

2. 5-Oxazolyl Homo C-Nucleosides

The only known example, **517**, was prepared by condensation of the D-mannono-1,4-lactone derivative **515** and the oxazole derivative **516** [77JCS(P1)743] (Scheme 133).



SCHEME 133



SCHEME 134

C. OXAZOLE CARBOCYCLIC C-NUCLEOSIDES

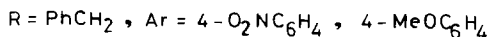
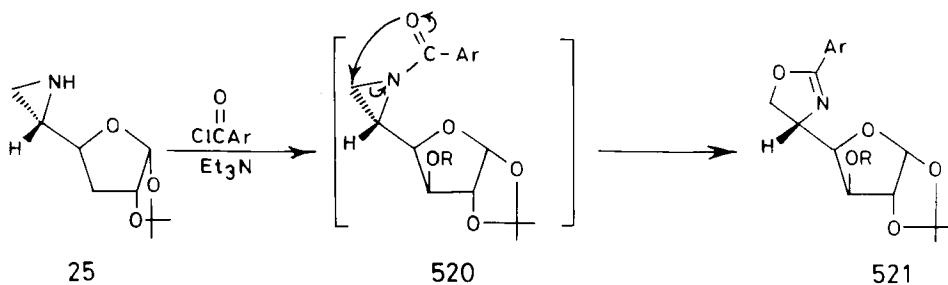
1. 2-Oxazolyl Carbocyclic C-Nucleosides

Similar to the synthesis of its sugar analog **506**, the 2-oxazolyl carbocyclic C-nucleoside **519** was prepared from the carbobicyclic hemiacetal **518** and 2-(methyamino)ethanol (76CJC849) (Scheme 134).

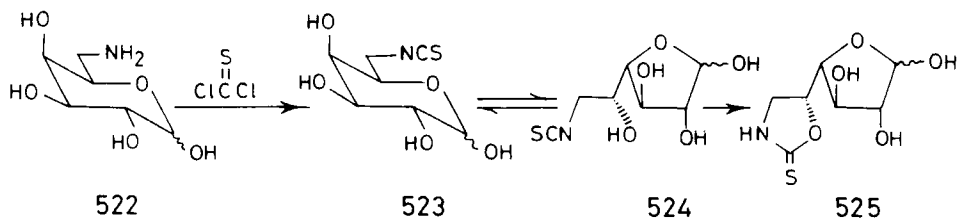
D. OXAZOLE REVERSE C-NUCLEOSIDES

1. 4-Oxazolyl Reverse C-Nucleosides

N-Aroylation of the azirino reverse C-nucleoside **25** took place with concomitant ring expansion isomerization to the (*S*)-4-oxazolyl reverse C-nucleoside **521** (70BCJ2501; 74CL519; 75BCJ610) (Scheme 135).



SCHEME 135



SCHEME 136

2. 5-Oxazolyl Reverse C-Nucleosides

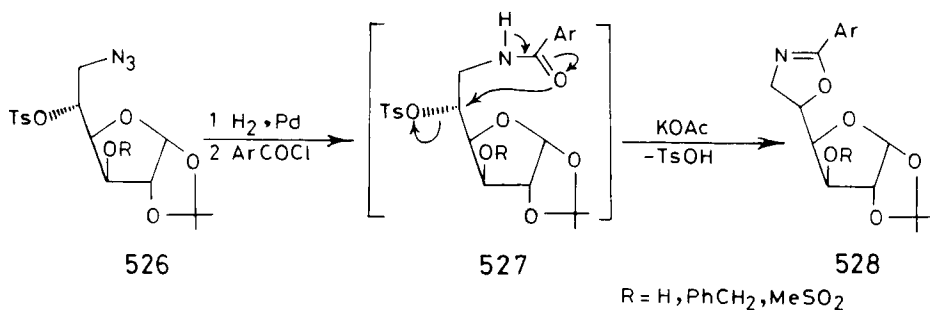
Thiophosgene selectively acylates the amino group of 6-amino-6-deoxy-D-galactopyranose (**522**) to give the thiocyanate derivative **523**, which spontaneously equilibrates to the furanose structure **524**. The latter cyclizes to the 2-thioxo-5-oxazolidinyl reverse C-nucleoside **625** (92TL3931; 93JOC5192) (Scheme 136).

Attempted displacement of the 4-tolylsulfonyloxy group of **527** with an acetoxy group culminated in the formation of the oxazole ring of **528** as a result of the participation of the neighboring arylamino group (68CB2294; 73JOC716; 75BCJ610) (Scheme 137).

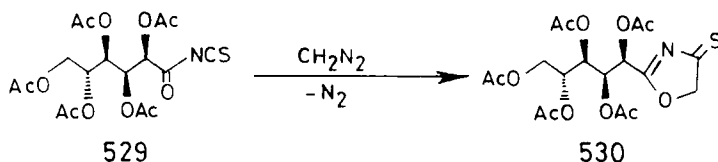
E. OXAZOLE ACYCLO C-NUCLEOSIDES

1. 2-Oxazolyl Acyclo C-Nucleosides

D-Gluconoylisoithiocyanate pentaacetate (**529**) reacted with diazomethane to give the 2-oxazolyl acyclo C-nucleoside **530** (81CPB1843) (Scheme 138).



SCHEME 137



SCHEME 138

2. 4-Oxazolyl Acyclo C-Nucleosides

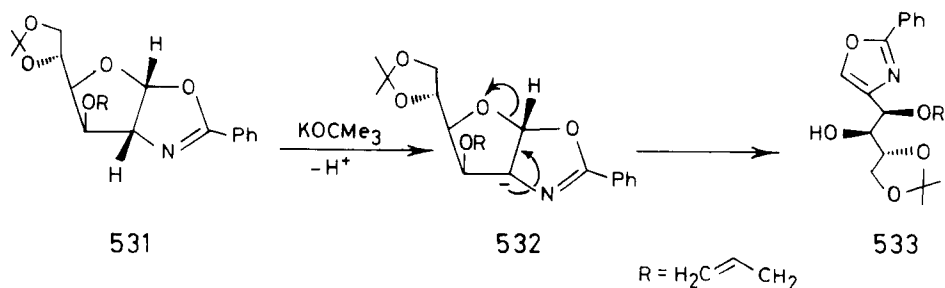
Synthesis of these compounds from nitrogen-containing sugar derivatives was achieved by rupture of the furan C1—O bond of the α-D-glucofuran-[2,1-*d*]oxazoline derivative **531** with alkali to give **533**. The reaction was initiated by abstraction of a proton from the oxazoline C4 [68JCS(C)1903] (Scheme 139).

Treatment of the *aldehydo*-D-mannosamine dithioacetal **534** with mercuric chloride caused its cyclization to the 4-oxazoliny acyclo C-nucleoside derivative **535** (88HCA609) (Scheme 140), and tri-*O*-methyl-D-glucosaminic acid (**536**) was easily cyclized to **537** by heating with trichloromethyl chloroformate (93MI7) (Scheme 141).

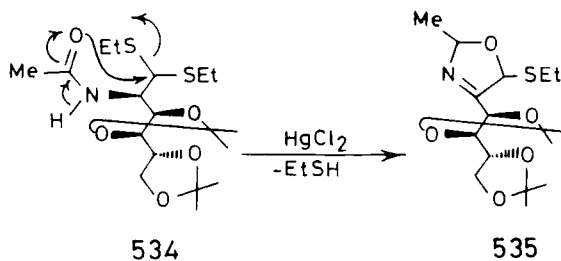
Synthesis from neutral sugar derivatives has been made by the reaction of D-fructose **538** and hydrothiocyanic acid to give **541** [88JCS(CC)671] [Scheme 142].

3. 5-Oxazolyl Acyclo C-Nucleosides

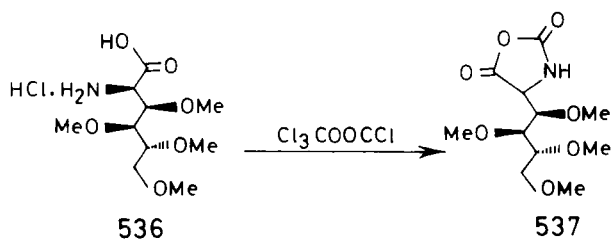
Intramolecular cyclization of the *N*-benzyloxycarbonylamino-D-glucose dithioacetal **542** with sodium methoxide gave the 5-(alditol-1-yl)oxazolidin-2-one **543** with elimination of a molecule of benzyl alcohol (67CB2655) (Scheme 143).



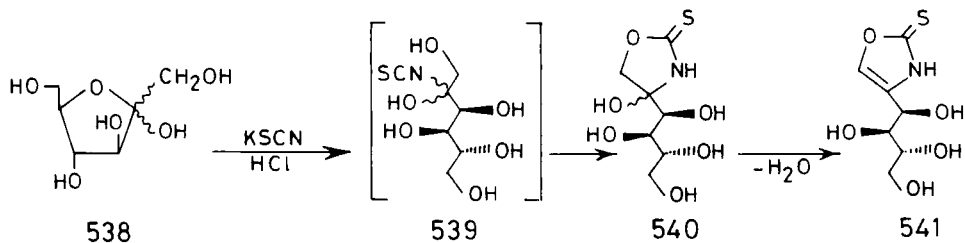
SCHEME 139



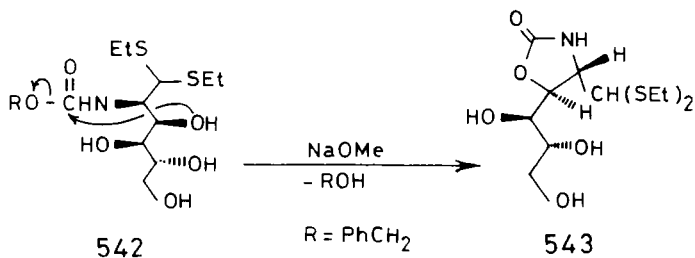
SCHEME 140



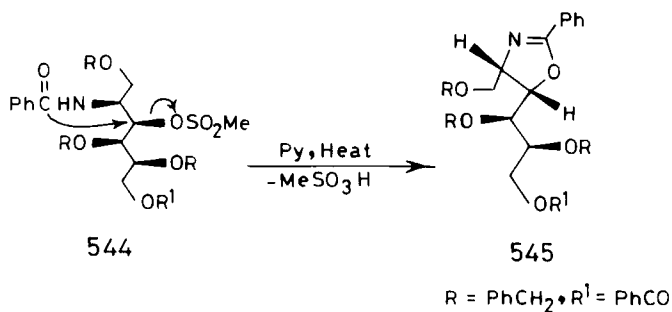
SCHEME 141



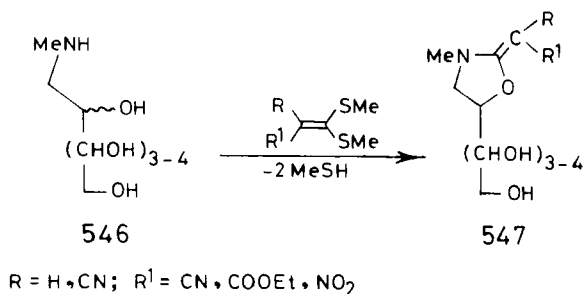
SCHEME 142



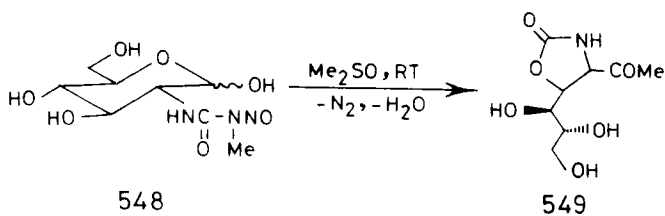
SCHEME 143



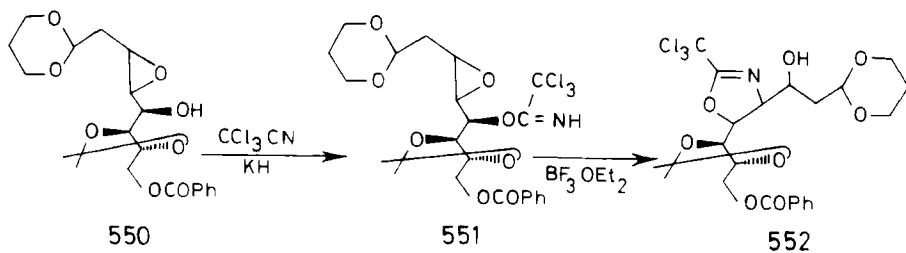
SCHEME 144



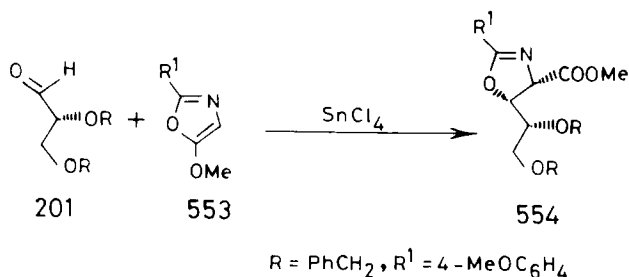
SCHEME 145



SCHEME 146



SCHEME 147



SCHEME 148

When the 2-benzamido-3-methylsulfonyloxy-L-iditol derivative **544** was heated with pyridine, the benzamido carbonyl attacked the back side of the carbon carrying the sulfonyloxy group to give the oxazoline **545** [63JOC442; 68JCS(C)2661] (Scheme 144).

1-Deoxy-1-methylaminoalditols (**546**) undergo condensative cyclization with benzaldehyde (71ZC306) or ketene dithioacetals (86JPR21) to 2-substituted 5-(alditol-1-yl)-3-methoxyoxazolidines (**547**) (Scheme 145).

Keeping a solution of the broad-spectrum antibiotic streptozocin **548** in dimethyl sulfoxide at ambient temperature caused loss of a nitrogen and a water molecule with concomitant intramolecular cyclization to the oxazol-5-yl acyclo C-nucleoside **549** (79JOC9) (Scheme 146).

Reaction of the *aldehydo*-octulose derivative **550** with trichloroacetonitrile gave **551**, which cyclized with boron trifluoride etherate to **552** (91MI12) (Scheme 147).

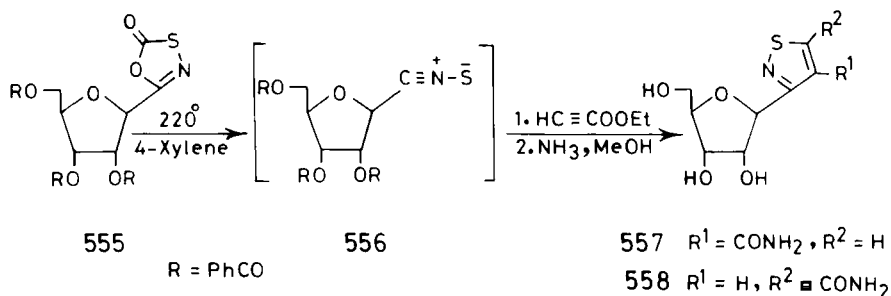
[3 + 2] Cycloaddition of 5-methoxy-2-anisiloxazole (**553**) with 2,3-di-*O*-benzyl-D-glyceraldehyde (**201**) in the presence of tin (IV) chloride took place with high (>95%) diastereoselectivity to give the oxazolin-5-yl acyclo C-nucleoside **554** (94JOC3359) (Scheme 148).

XI. 1,2-Thiazole C-Nucleosides

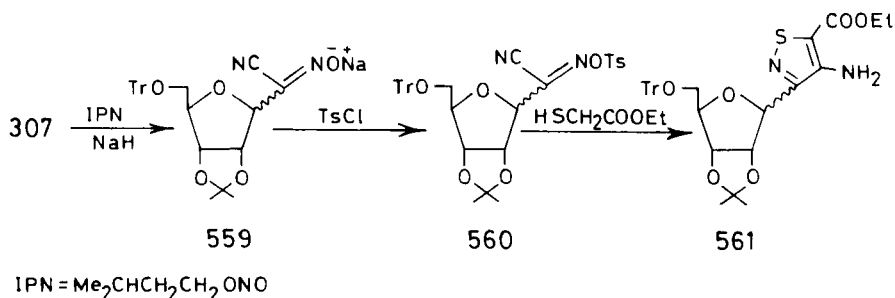
A. ISOTHIAZOLE C-NUCLEOSIDES

1. 3-Isothiazolyl C-Nucleosides

The 2,5-anhydro-D-allononitrile *N*-sulfide **556**, obtained by the thermolysis of the 5-(β-D-ribofuranosyl)-1,3,4-oxathiazol-2-one **555** (Section XXI; Scheme 213), underwent 1,3-dipolar cycloaddition with ethyl acetylenecarboxylate to give, after de-*O*-protection and amidation, a mixture of the



SCHEME 149



SCHEME 150

4-carboxamido- and 5-carboxamido-3-(β -D-ribofuranosyl)isothiazoles **557** and **558** (84JOC2165; 91MI21, 94MI9) (Scheme 149).

Regioselective C-nitrosation of the D-ribofuranosylacetonitrile derivative **307** with isopentyl nitrite (IPN) in the presence of sodium hydride gave **559**. Tosylation of **559** gave the 2-tosyloximino derivative **560**, which condensed with ethyl mercaptoacetate to give a mixture of the anomeric 3-isothiazolyl C-nucleosides **561** (93JOC5181) (Scheme 150). The isothiazole C-nucleosides **557**, **558**, and **561** were tested for antitumor and antiviral activities but were found inactive (84JOC2165; 93JOC5181; 94MI9).

XII. 1,3-Thiazole and 1,3-Selenazole C-Nucleosides

Because of the close similarities of their methods of preparation and their properties, these two categories of C-nucleosides are reviewed together.

A. THIAZOLE AND SELENAZOLE C-NUCLEOSIDES

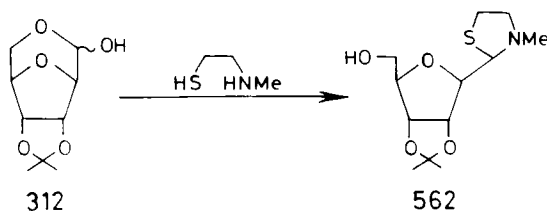
1. 2-Thiazolyl and 2-Selenazolyl C-Nucleosides

Cyclocondensation of the bicyclic 2,5-anhydro-D-allose derivative **312** with 2-(methylamino)thioethanol gave the 2- β -D-ribofuranosylthiazolidine **562** (75CJC131) (Scheme 151). The 2- β -D-arabinofuranosylthiazolidine isomer of **562** was prepared in the same way (80CJC2024).

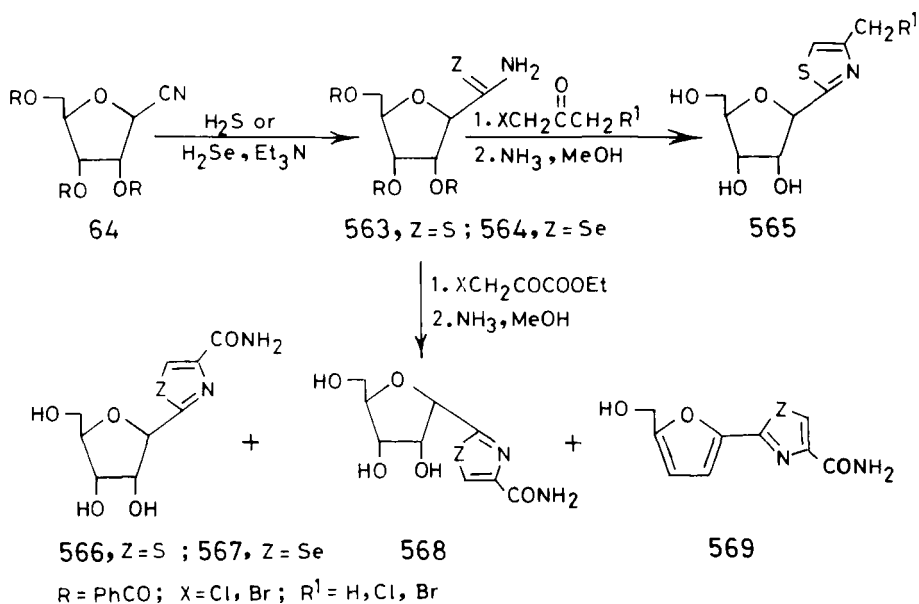
Many 2-thiazolyl C-nucleosides (**565**) were prepared by the Hantzsch reaction of the β -D-ribofuranosylthioamide **563** with α -haloketones (75MI8; 77JMC256; 82MI16; 83MIP1). 4-Carboxamido-2- β -D-ribofuranosylthiazole (**566**), the first synthetic C-nucleoside with outstanding antiviral and antitumor activities, was obtained in 1976 by Spanish investigators upon condensation of the thiocarboxamide **563** with ethyl bromopyruvate followed by concurrent de-*O*-benzoylation and amidation (76JOC4074). One year later, R. K. Robins and his group reported (77JMC256) the preparation of **566**, together with its α -anomer **568**, using the same protocol and gave it the generic name "tiazofurin." Realizing the potential of the various biological activities of tiazofurin, the same group synthesized the selenium analog (**567**) from the selenocarboxamide **564** and generically named it "selenazofurin" (83JMC445) (Scheme 152).

Since then, articles have described the preparation of tiazofurin **566** from **563** (83EUP72977; 91MI22) and from totally unprotected β -D-ribofuranosylthiocarboxamide (85JOC1741). The latter derivative was used to avoid the formation of unsaturated derivative **569** as a result of elimination reactions that take place when the *O*-benzoylated thiocarboxamide was used (77JMC256). Similar syntheses of selenazole (85JOC1741; 86EUP171171, 86JHC155) and $^{14}\text{C}2$ -labeled selenazole (**572**) (88MI1) were published (Scheme 153).

An interesting synthesis of tiazofurin is that in which the penicillinate derivative **573** was condensed with the 2,5-anhydro-D-allonoyl chloride **507**



SCHEME 151

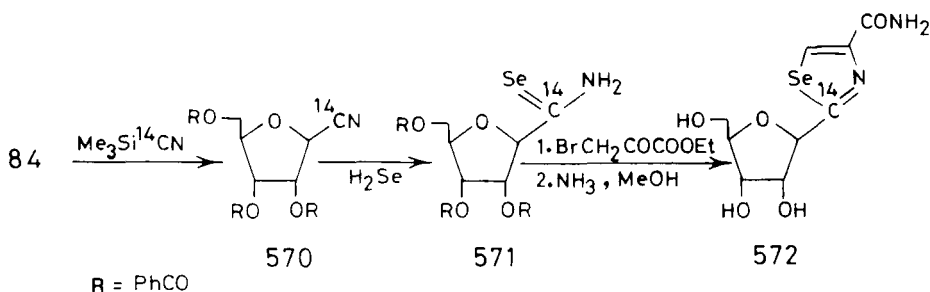


SCHEME 152

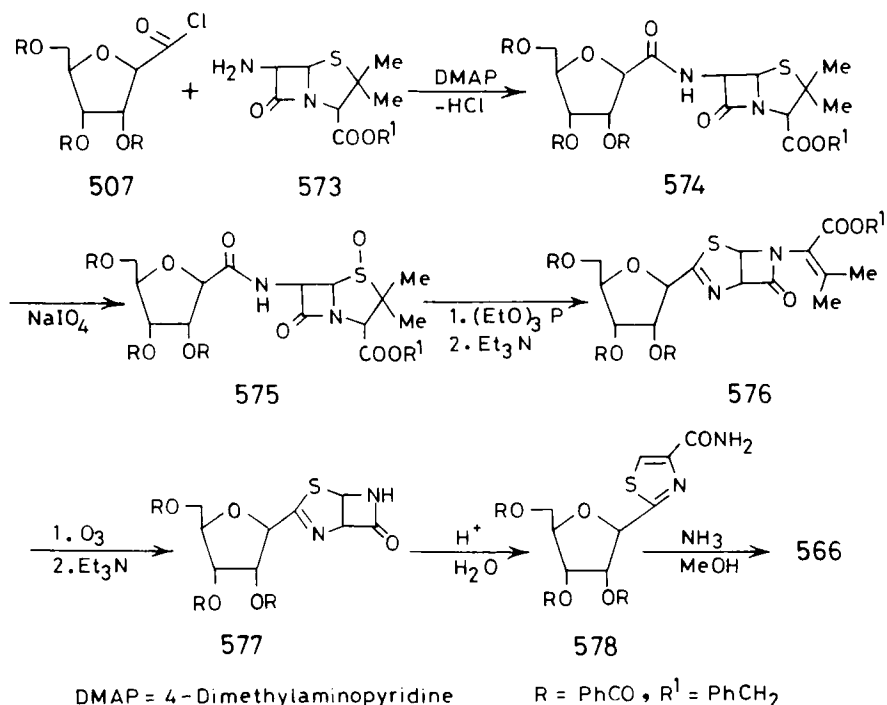
to give the 2,5-*anhydro*-D-allonoyl-penicilline derivative **574**, which was then elaborated to **566** [90JCS(P1)283] (Scheme 154).

Recently an example of 2-thiazolyl *C*-nucleoside has been prepared by acid-catalyzed cyclodehydration of its acyclo analog (94JA3325).

With the aim of studying the structure–biological activity relationship, many permutations of thiazofurin that comprised variations in both the sugar and thiazole subunits were prepared. Among the sugar-modified thiazofurins,

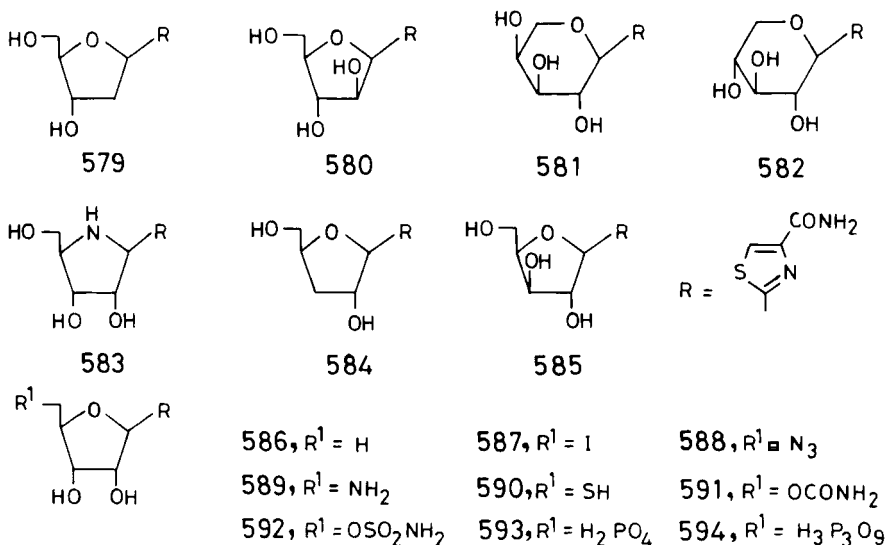


SCHEME 153

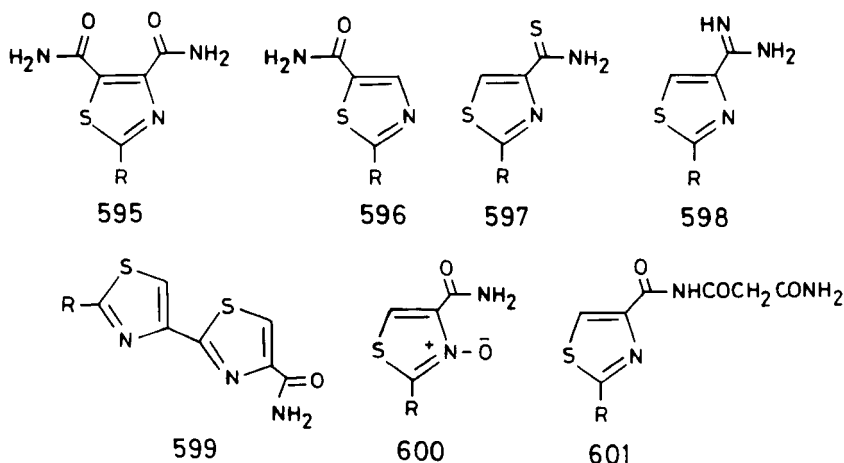


SCHEME 154

obtained from the appropriate sugar thiocarboxamides, were 2'-deoxytiazofurin (**579**) and its α -anomer (81JHC1659), 2- β -D-arabinofuranosyl-4-carboxamidothiazole (*ara*-tiazofurin) (**580**) and its α -anomer (84MI9), 4-carboxamido-2- α -L-arabinopyranosylthiazole (**581**), 4-carboxamido-2- β -D-xylopyranosylthiazole (**582**) (91T5539, 91T5549), and the analog having a nitrogen-containing sugar moiety **583** (86JOC4436). Sugar-modified tiazofurins that were prepared by deoxygenation or inversion of configuration at one carbon or more of the sugar moiety included 3'-deoxytiazofurin (**584**) (84MI7), *ara*-tiazofurin (**580**) (84TL2111), and 4-carboxamido-2- β -D-xylofuranosylthiazole (**585**) (84TL2111). 5'-Modified tiazofurins comprised 5'-deoxy- (**586**) and 5'-deoxy-5'-iodotiazofurin (**587**) (77JMC256); 5'-azido-5'-deoxy- (**588**), 5'-amino-5'-deoxy- (**589**), and 5'-deoxy-5'-mercaptotiazofurin (**590**) (86MI6); 5'-*O*-carbamoyl- (**591**) and 5'-*O*-sulfamoyltiazofurin (**592**) (86MI7); and tiazofurin 5'-mono- (**593**) and 5'-triphosphates (**594**) (84JMC266). A few long-chain *O*-acylated derivatives of tiazofurin were also prepared and found useful as inhibitors of malignant tumors in warm-blooded animals (82EUP54432).



Tiazofurin-related *C*-nucleosides modified in the thiazole ring included 4,5-dicarboxamido- (**595**) (76JOC4074), 5-carboxamido- (**596**), 4-thiocarboxamido- (**597**) (77JMC256), 4-carboxamidino- (**598**) (84JMC266, 84USP4461891), 4-(4-carboxamidothiazol-2-yl)- (**599**) (84JMC266), 4-carboxamido-*N*³-oxide (**600**) (85MI13), and 4-carboxyglycinamidothiazol-2-yl (**601**) (91MI23) *C*-nucleosides.



$R = \beta\text{-D-ribofuranosyl}$

X-ray and computational structural analyses of tiazofurin and selenazofurin and their analogs revealed that the thiazole and selenazole rings are almost planar and the presence of intramolecular electrostatic interaction between the positively charged S or Se atom and the negatively charged oxygen of the ribofuranosyl ring. This electrostatic interaction caused rotational restriction about the glycosidic bond and close contact between the heterocyclic and sugar rings [81JHC1659; 83JA7416; 85JA1394, 85MI13; 88JMC1026; 91AX(C)1272; 92AX(B)677, 92JA2313, 92JMC3560].

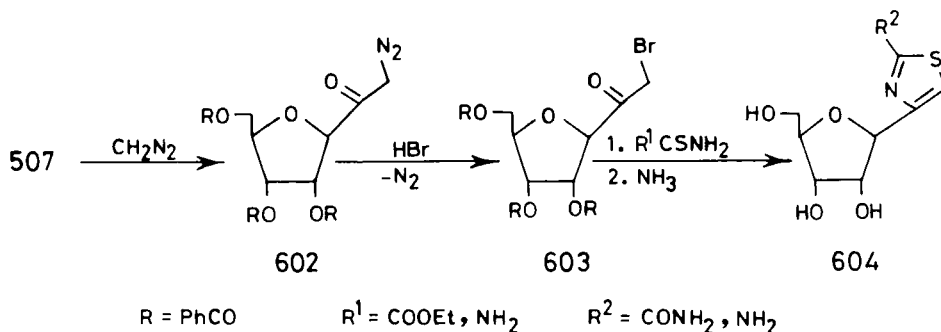
Both tiazofurin and selenazofurin are highly effective against viruses (77JMC256; 83AAC353; 84AAC476; 85AAC375) various types of leukemias [82EUP54432, 82MI1, 82MI14; 83BBR(115)544, 83BBR(115)971, 83JMC445, 83MI6; 84JMC266; 87MI1, 87MI2; 89MI1, 89MI2, 89MI5; 90MI1, 90MI2; 91MI3, 91MI4; 92MI5], Lewis lung cancer (82JMC107, 82MI2; 83JMC445), breast cancer (89MI1), ovarian cancer (85MI2), and colon cancer (92MI2). It has been found that although both nucleosides have the same spectrum of antitumor activity, selenazofurin is severalfold more cytotoxic than tiazofurin [83BBR(115)544]. Most modifications in the tiazofurin structure, whether in the thiazole or sugar moieties, seemed to nullify cytotoxicity. Of the several modifications in the thiazole ring, only the carboxamide derivatives **598** retained slight antitumor activity. Of the sugar ring modified analogs, only 3'-deoxytiazofurin (**584**) retained moderate activity against P388 leukemia (84TL2111). It has been concluded that the β -D-ribofuranosyl sugar moiety and the 4-carboxamidothiazol-2-yl moieties are indispensable features for biological activities of tiazofurin. Biologically, tiazofurin and selenazofurin appear to block the vital process of guanine-nucleotide biosynthesis as a result of being metabolized as tiazofurin-adenine and selenazofurin-adenine dinucleotides [82BBR(107)862; 87MI2; 89MI5, 90MI2; 91MI3], both of which inhibit inosine monophosphate dehydrogenase (82MI2; 83MI3, 83MI4; 85MI1; 86MI2; 88B2193), the enzyme catalyzing the rate-determining step of guanine-nucleotide synthesis.

2. 4-Thiazolyl C-Nucleosides

The 2-substituted-4- β -D-ribofuranosylthiazoles (**604**) were prepared by cyclocondensation of the bromomethyl-(β -D-ribofuranosyl)ketone derivative **603** with thiocarboxamides (79CCC1339, 79MI2; 92SC2815) (Scheme 155).

3. 5-Thiazolyl C-Nucleosides

α -Halo- α -glycosyl-aldehydes and ketones (**605**) gave the 5-glycosylthiazoles **606** when cyclocondensed with thiocarboxamides (79JOC4351; 83JOC3141) (Scheme 156).



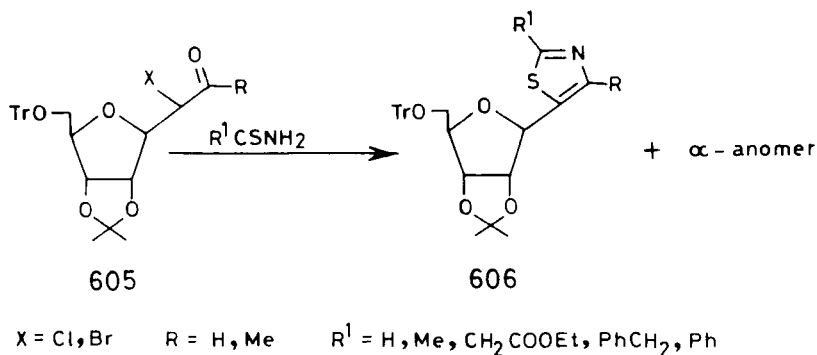
SCHEME 155

The 5-(2-deoxy- β -D-ribofuranosyl)thiazole **607** was obtained when compound **384** was treated with hydrogen sulfide followed by ammonia [95JCS(P1)3029] (Scheme 157).

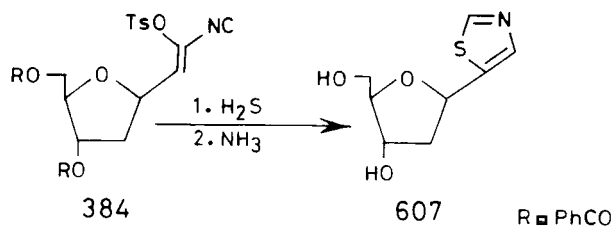
B. THIAZOLE CARBOCYCLIC C-NUCLEOSIDES

1. 2-Thiazolyl Carbocyclic C-Nucleosides

Only 2-thiazolyl carbocyclic C-nucleosides have been synthesized as yet. The two known examples of this genre are the carbocyclic C-nucleoside analog of the 2-thiazolidinyl C-nucleoside **562** (76CJC849) and the carbocyclic analog of tiazofurin (**566**) [93JCS(P1)57]. They were synthesized in similar steps from the carbocyclic analogs of the thioamides **312** and **563**, respectively.



SCHEME 156



SCHEME 157

C. THIAZOLE REVERSE C-NUCLEOSIDES

1. 2-Thiazolyl Reverse C-Nucleosides

Diastereoselective addition of 2-trimethylsilylthiazole to sugar derivatives having a tail aldehyde function such as **608** gave the corresponding reverse C-nucleosides **609** and **610** (87T3539; 89JOC693; 94CJC237) (Scheme 158).

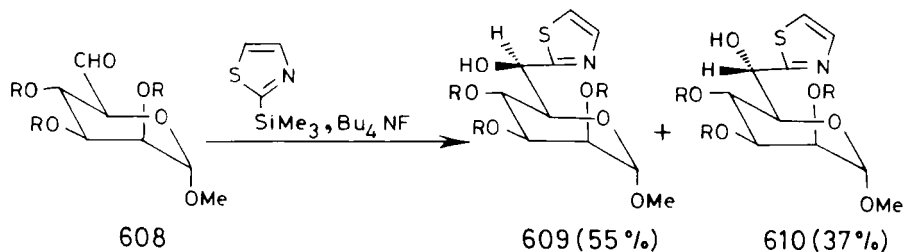
2. 4-Thiazolyl Reverse C-Nucleosides

Treatment of the azirine reverse C-nucleoside **25** or its *N*-benzoyl derivative with carbon disulfide gave the 4-thiazolyl reverse C-nucleoside **611** (74CL519; 75BCJ610) (Scheme 159).

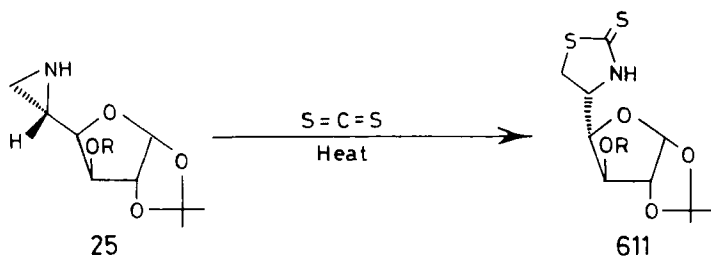
Reaction of 6-halo-5-ketofuranose derivatives such as **612** (75HCA1507) or 6-diazo-5-ketohexofuranoses (76JOC4074) with thioamides gave products (**613**) that belong to this type of C-nucleosides (Scheme 160).

3. 5-Thiazolyl Reverse C-Nucleosides

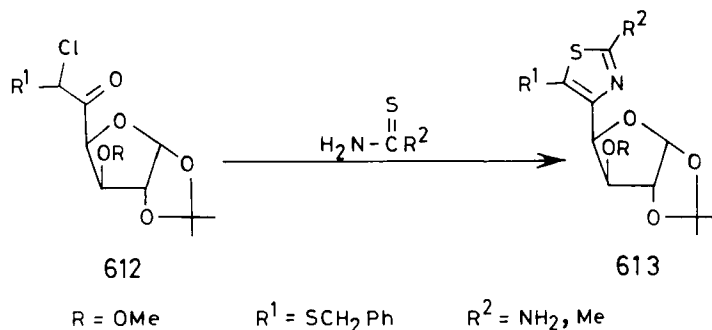
Carbon disulfide attacked the amino group of **614** followed by back-side displacement of the neighboring sulfonyloxy group to give the 5-thiazolidinyl reverse C-nucleoside **616** (75BCJ610) (Scheme 161).



SCHEME 158



SCHEME 159

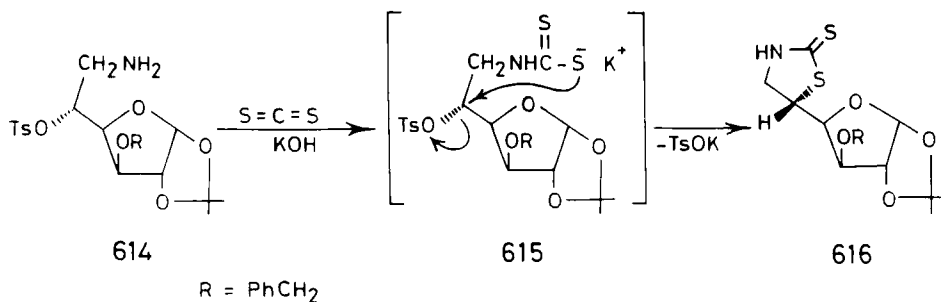


SCHEME 160

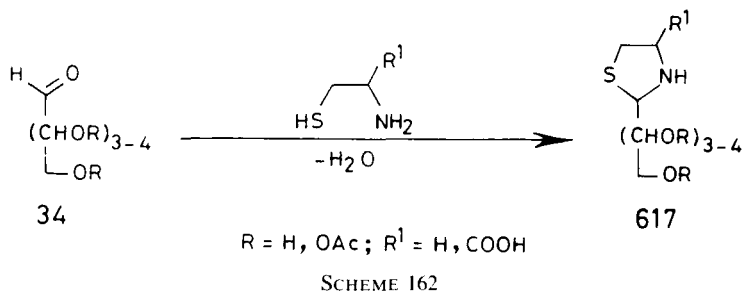
D. THIAZOLE ACYCLO C-NUCLEOSIDES

1. 2-Thiazolyl Acyclo C-Nucleosides

The earliest synthesis of members of these analogs (**617**) involved reaction of aldose sugars (**34**) with L-cysteine (39JBC601; 53MI1; 75LA1637; 76-LA450) or 2-aminoethanethiol (61CB225) (Scheme 162).

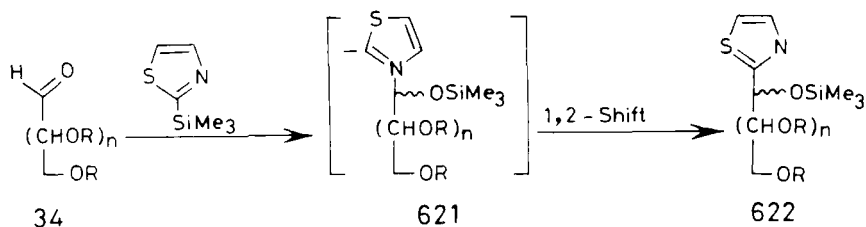
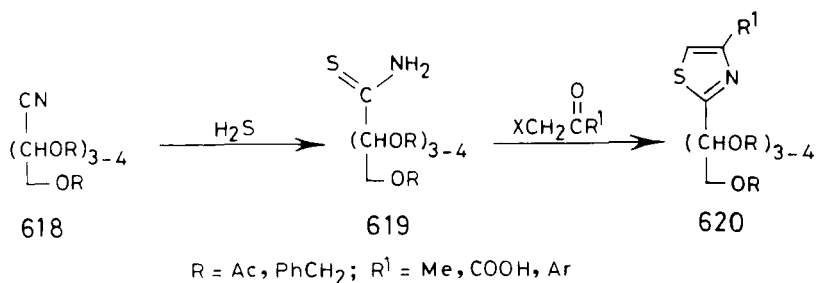


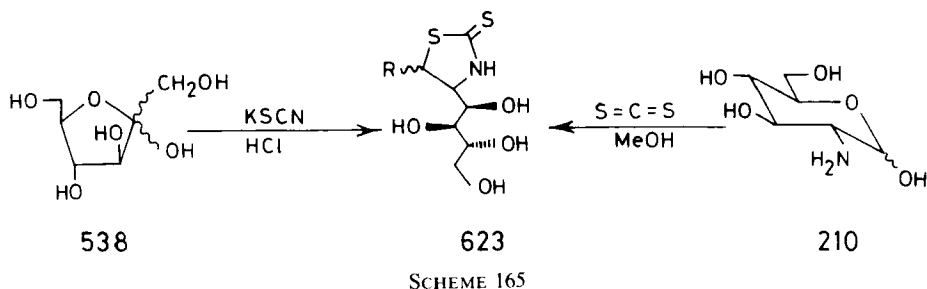
SCHEME 161



Aldonic acid thioamide acetates (**619**) condensed with various α -halo-ketones to afford the 2-(alditol-1-yl)thiazoles **620** [54AQ(B)609, 54CB78; 69ACH(62)179, 69T3413; 87H947; 95TL3781] (Scheme 163).

Utilizing the 2-thiazolyl moiety to serve as a potential aldehyde function, Dondoni and his co-workers prepared many 2-(alditol-1-yl)thiazoles (**622**) during their studies on homologation of monosaccharides. Compounds **622** were obtained by addition of *aldehyde*-sugar derivatives (**34**) to 2-trimethylsilylthiazole (85TL5477; 89JOC693, 89JOC720) or 2-thiazolylphosphorus ylides (93T2939; 94JA3325) (Scheme 164).

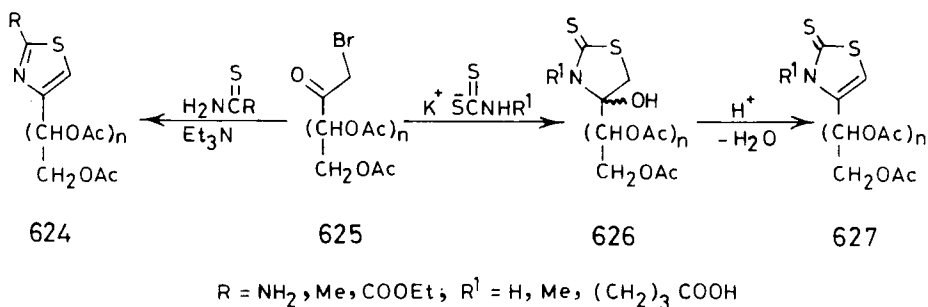




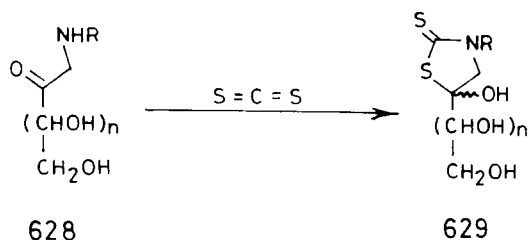
2. 4-Thiazolyl Acyclo C-Nucleosides

It has been mentioned previously (Section X,E,2) that D-fructose (**538**) reacted with hydrothiocyanic acid to give the 4-(D-arabino-tetritol-1-yl)oxazole-2-thione (**541**) [88JCS(CC)671]. Other authors (38CB590; 66AG980), however, reported that this reaction afforded the 4-(D-arabino-tetritol-1-yl)thiazoline-2-thione (**623**, R = H). The 5-hydroxy derivative **623** (R = OH) was obtained when D-glucosamine (**210**) was cyclized with carbon disulfide (66AGE964) (Scheme 165).

1-Halo-1-deoxy-2-ketose acetates (**625**) react with thioamides [57AQ(B) 705, 57CI(L)666; 75MI8; 79CCC1339] or dithiocarbamates (68MI5, 68MI7) to give the corresponding 3-substituted 4-(alditol-1-yl)thiazoles **624** or thiazoline-3-thiones (**627**), respectively (Scheme 166). 3-Arylamino-2-cyano-3-mercaptoacrylates react with **625** to give 3-alkylidene-4-(alditol-1-yl)-3-arylthiazoles [84GEP(D)216458; 86PHA548].



SCHEME 166

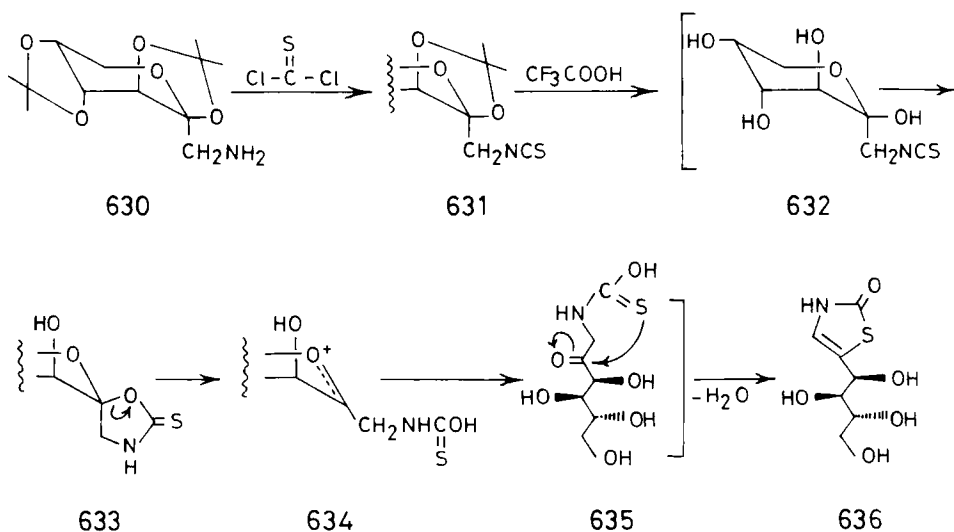


SCHEME 167

3. 5-Thiazolyl Acyclo C-Nucleosides

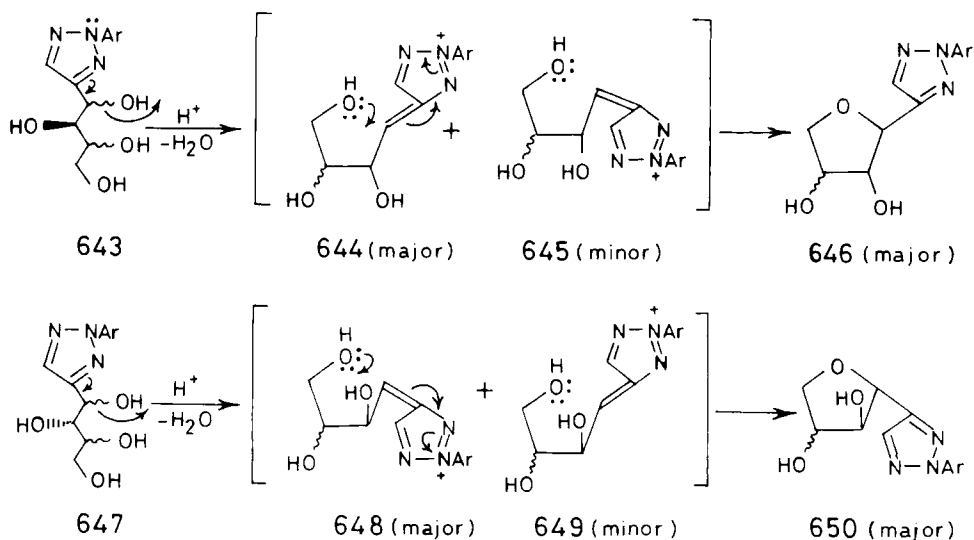
Reaction of 1-amino-1-deoxy-2-ketoses (**628**) with carbon disulfide gave the 5-(alditol-1-yl)-5-hydroxythiazolidines **629** (66AJC445; 75CB2320; 90AQ675) (Scheme 167).

O-Protected 1-deoxy-1-thiocyanato-2-ketoses such as **631** gave, upon de-O-protection, 5-(alditol-1-yl)thiazolin-2-ones (**636**) (94MI6) (Scheme 168).



SCHEME 168

SCHEME 169



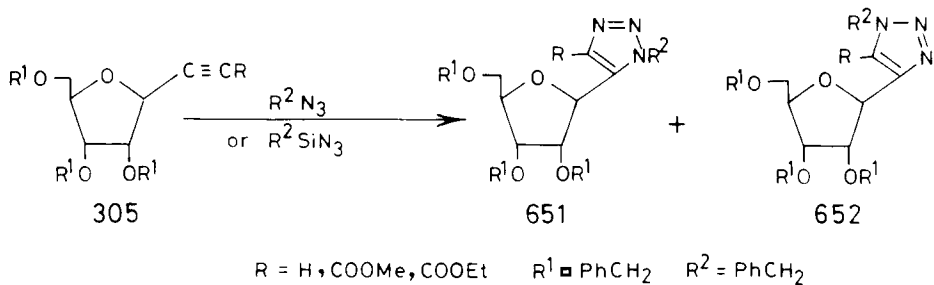
SCHEME 170

gave a mixture of the two 1,2,3-triazole C-nucleoside isomers **651** and **652** (Scheme 171).

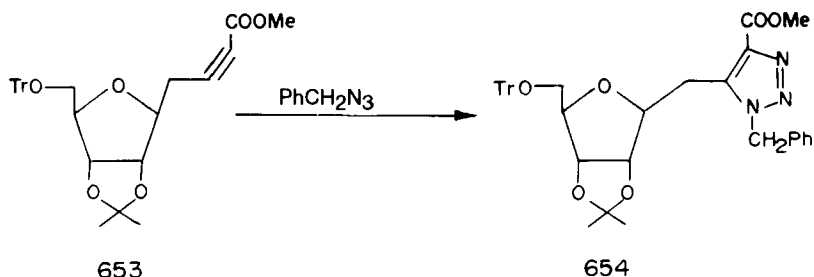
B. 1,2,3-TRIAZOLE HOMO C-NUCLEOSIDES

Benzyl azide added to the 4-(β -D-ribofuranosyl)but-2-ynoate derivative **536** to afford **654** (90MI9) (Scheme 172).

4-(D-galacto-Pentitol-1-yl)-2-phenyl-1,2,3-triazole (**655**) underwent intramolecular cyclodehydration and concurrent O-4-toluenesulfonylation when treated with 4-toluenesulfonyl chloride to give the derivatized 1,2,3-triazole homo C-nucleosides **656–658** [95JCR(S)54] (Scheme 173).



SCHEME 171



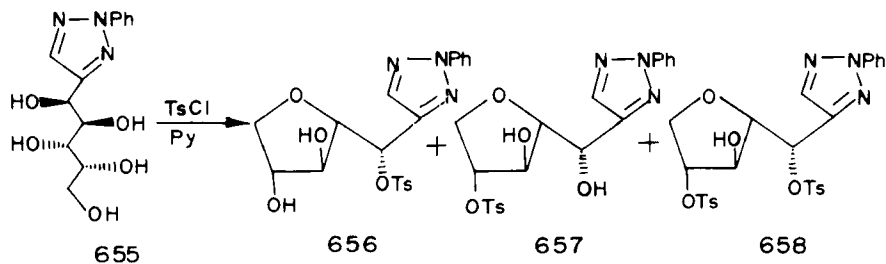
SCHEME 172

C. 1,2,3-TRIAZOLE REVERSE C-NUCLEOSIDES

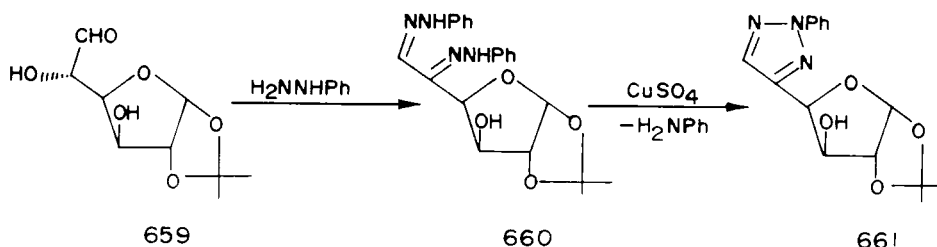
Analog of this type (**661** and **663**) were prepared by cyclization of the reverse phenylosazone **660** by heating with aqueous copper(II) sulfate (68CB2074) (Scheme 174) or by cycloaddition of phenyl azide to the acetylenic sugar derivative **662** [71MI1] (Scheme 175).

D. 1,2,3-TRIAZOLE ACYCLO C-NUCLEOSIDES

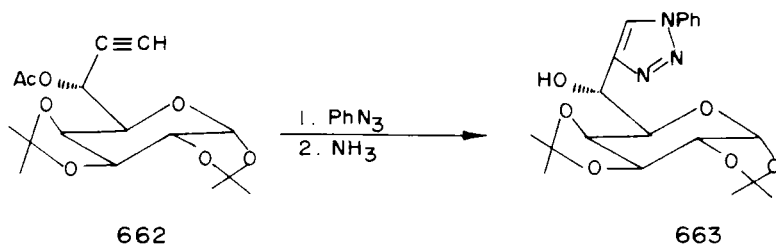
Systematically, these compounds are 4(5)-alditol-1-yl)-1,2,3-triazoles; trivially, they are known as osotriazoles. They are the most extensively studied class of carbohydrate 1,2,3-triazole derivatives (63MI1; 65MI1; 70MI1). The first of these compounds, 2-phenyl-4-(D-*arabino*-tetritol-1-yl)-1,2,3-triazole (**665**), was obtained by Hann and Hudson (44JA735) upon investigating the action of copper(II) sulfate on D-glucose phenylosazone (**664**). Compound **665** was formed from **664** through loss of an aniline molecule, and its structure was confirmed by oxidation to 4-formyl-2-phenyl-1,2,3-triazole (**666**) (Scheme 176). Thereafter, many monosaccharide 2-arylosotriazoles (45JA939; 46JA1766; 47HCA900, 47HCA1478,



SCHEME 173

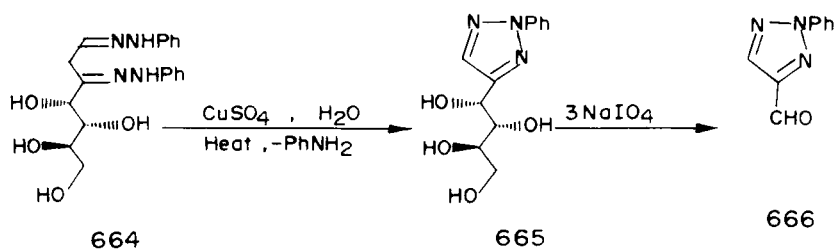


SCHEME 174

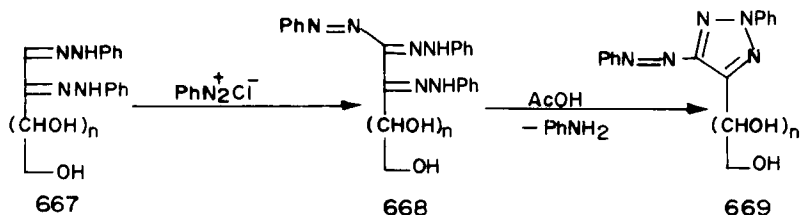


SCHEME 175

47JA246, 47JA1050, 47JA1461; 51HCA253; 52JA2206, 52JA2210; 53-JA4320, 53JCS3452; 56CB1167; 62JOC1892; 63JCS3531, 63JCS4980; 68CB2074; 71MI4; 72CB954; 73MI7) and reducing disaccharide 2-arylosotriazoles (44JOC470; 47JA1461, 47MI1; 48JA306, 48JA2288; 52JA3202; 54JA5173; 56JA2514; 69MI6) were similarly prepared by cyclization of the corresponding arylosazones. Cyclization of osazones has also been effected using enzymes (49CCC80), potassium nitrosodisulfonate (52CB95), nitrous acid (57ACH173; 64JOC2072), copper(II) chloride, nitrate, or acetate, iron(III) chloride or sulfate, potassium ferricyanide (58JCS3117), bromine in water (58JCS3117; 59JCS1655; 60JCS3993; 62JCS3154; 65JCS1524), chlorine in water, or iodine in aqueous potassium iodide (61JCS2957).



SCHEME 176



SCHEME 177

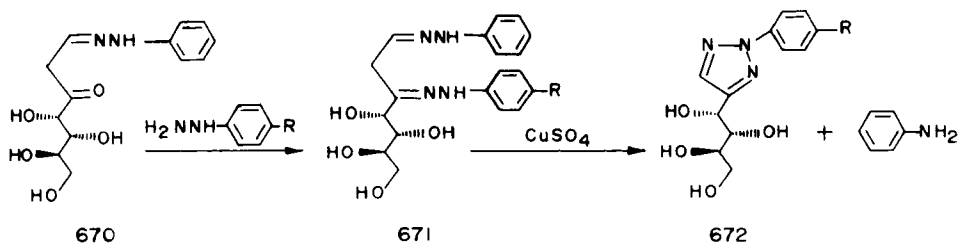
4-(Alditol-1-yl)-2-phenyl-5-phenylazo-1,2,3-triazoles (osotriazole formazans) (**669**) were obtained by cyclization of the corresponding osazone formazans (**668**) with acetic acid (60BSF350; 62BSF381) (Scheme 177).

^{82}Br -labeled osazones were used to establish that the arylamine molecule departing during cyclization of osazones invariably originated from the C-1 arylhydrazone residue (55CB487). This result was further confirmed by cyclizing mixed osazones (**671**) and identifying the resulting osotriazole and arylamine (60CB45) (Scheme 178).

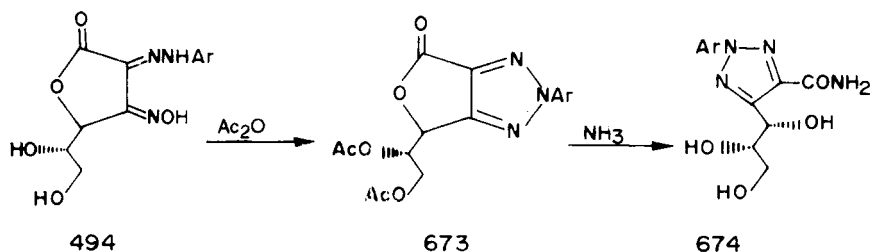
4-(Alditol-1-yl)-2-aryl-5-carboxamido-1,2,3-triazoles (**674**) were prepared from dehydro-L-ascorbic acid 2-arylhydrazone-3-oximes (**494**) by heating with acetic anhydride and then treating with ammonia (77MI8; 82MI13; 83MI8; 93MI1) (Scheme 179).

Attempted cyclization of monosaccharide aroylasazones (**676**) by heating with aqueous copper(II) sulfate caused splitting of the two aroylhydrazone residues and regenerated the starting sugar osones (**676**). Oxidative cyclization of the *O*-acetyl derivatives of these osazones, however, with iodine and yellow mercury(II) oxide gave the acetyl derivatives of 4-(alditol-1-yl)-1-aroynamino-1,2,3-triazole enol aroylates **677** [66MI4; 67JCS(C)519; 68JCS(C)1465] (Scheme 180).

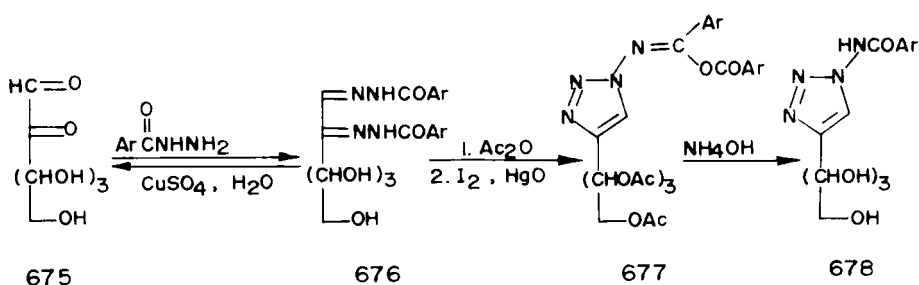
Addition of phenyl azide to acyclo acetylenic sugar derivatives such as **679** gave a mixture of 1-phenyl-4- and 5-(alditol-1-yl)-1,2-3-triazole derivatives (**680**, **681**) (76MI10) (Scheme 181).



SCHEME 178

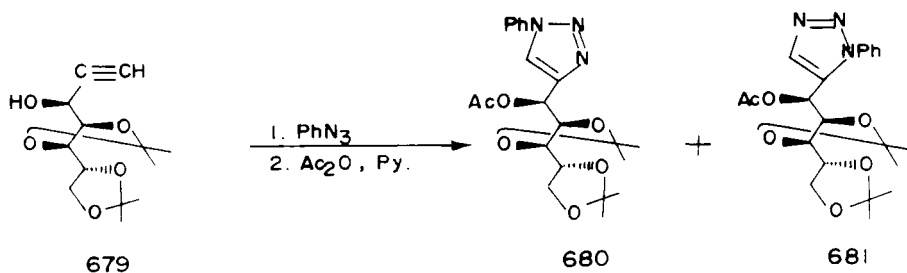


SCHEME 179



SCHEME 180

The configurational-conformational relationships in 1,2,3-triazole acyclo C-nucleosides have been studied using ^1H NMR (68JOC734; 72JOC1630), ORD, and CD spectra (68JOC2478). Some empirical rules were devised to correlate the sign of their optical rotation with the configuration at C-2 of the alditolyl chain (63JOC2478; 64AJC227). Application of some 4-(alditol-1-yl)-2-(4-aminophenyl)-1,2,3-triazoles as azo dyes with good affinity to cellulosic fibers has been explored (62NAT373; 63JCS3528).



SCHEME 181

XIV. 1,2,4-Triazole C-Nucleosides

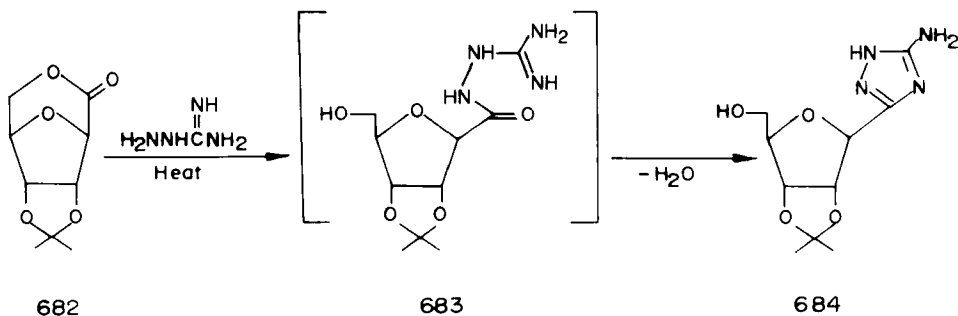
A. 1,2,4-TRIAZOLE C-NUCLEOSIDES

Mostly, these compounds were synthesized by cyclocondensation of aldonic acid derivatives, such as lactones, imidate esters, or thioimide esters, with acylhydrazines. Thus, reaction of the 2,5-anhydro-D-allono-1,6-lactone derivative **682** with aminoguanidine gave the 3-amino-5-(β -D-ribofuranosyl)-1,2,4-triazole **684** (75TL985) (Scheme 182).

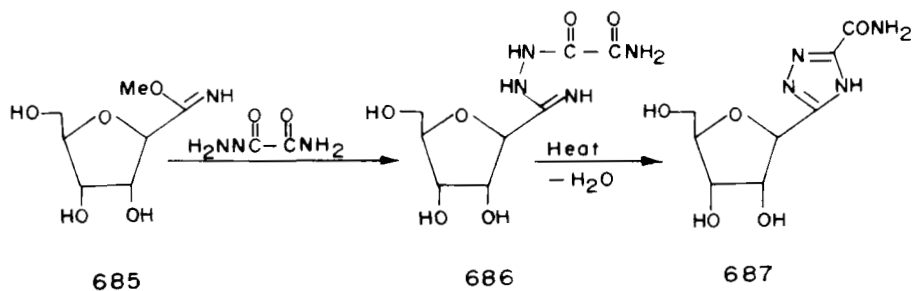
3-Carboxamido-5-(β -D-ribofuranosyl)-1,2,4-triazole (**687**), the C-analog of the synthetic N-nucleoside "ribavirin" [3-carboxamido-1-(β -D-ribofuranosyl)-1,2,4-triazole] with pronounced biological activities, was prepared by cyclization of the imidate **685** (77JOC1109; 80JOC203) or the corresponding O-benzoylated thioimide [77JCS(P1)761; 79CCC1334, 79MI1] with oxamic acid hydrazide (Scheme 183). Unlike ribavirin, its C-nucleoside analog **687** did not inhibit viral replication [77JCS(P1)761; 79CCC1334]. Acetylation and subsequent dehydration of **687** gave the nitrile **688** (77JOC1109), which was partially converted to the amidine **690** (88JMC330). The amidine **690** did not inhibit inosine phosphorolysis (88JMC330) (Scheme 184).

Reaction of the imidate **685** with thiosemicarbazide gave **691**, which cyclized to the 4-(β -D-ribofuranosyl)-5-thioxo-1,2,4-triazole **692** and not the 3-amino-5-(β -D-ribofuranosyl)-1,3,4-thiadiazole **693** (80JOC203) (Scheme 185).

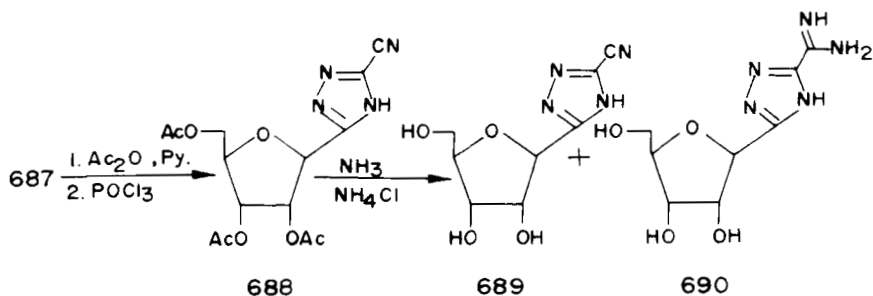
Interchanging functionalities of the reacting species in the aforementioned reaction, that is, reacting sugar amidrazones (**694**) with acid derivatives such as ethyl oxamate, has also been used to synthesize 1,2,4-triazole C-nucleosides such as **696** (91MI26) (Scheme 186).



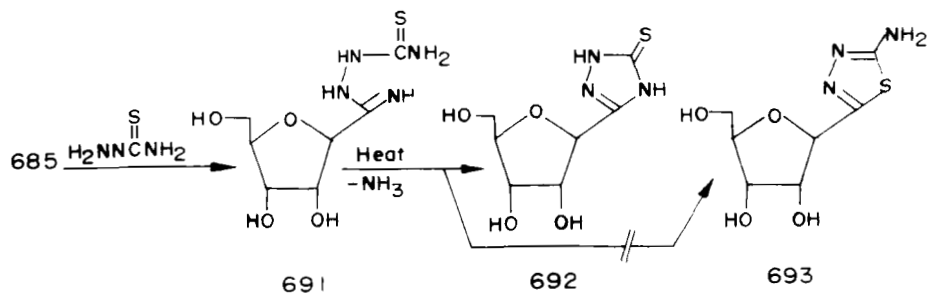
SCHEME 182



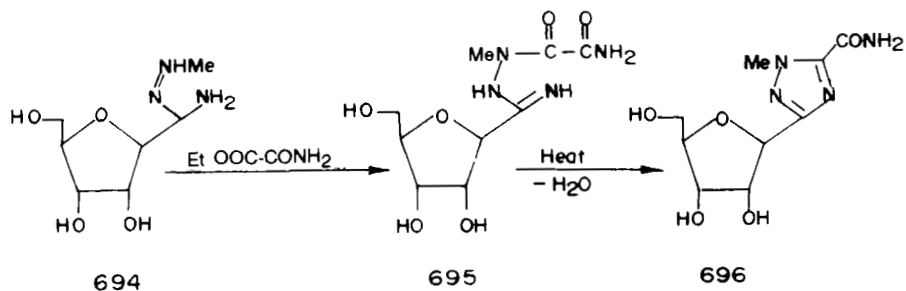
SCHEME 183



SCHEME 184



SCHEME 185



SCHEME 186

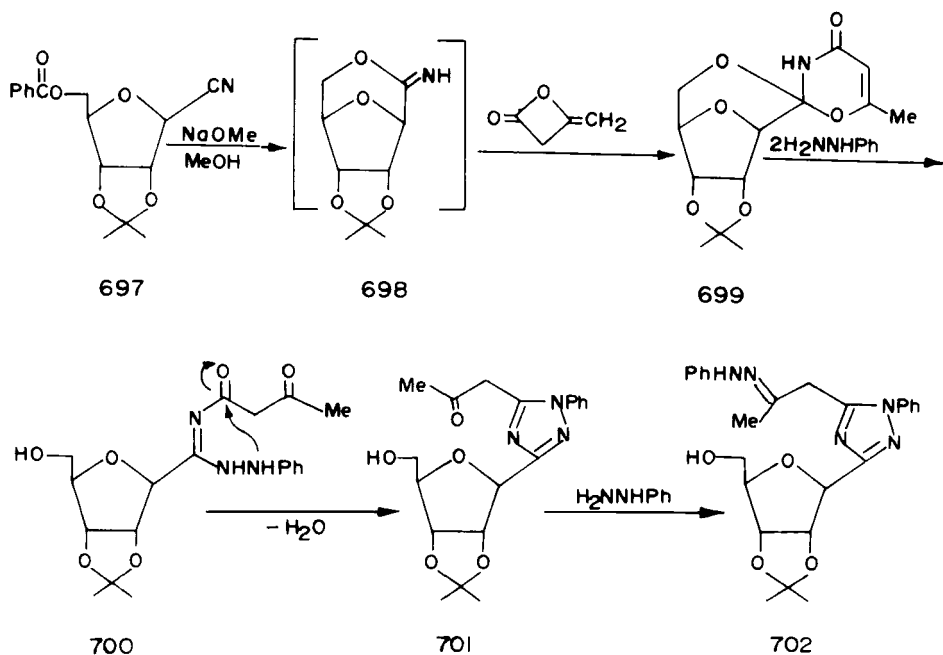
Oxazine ring opening of the sugar spiro derivative **699** with phenylhydrazine gave the 1,2,4-triazole *C*-nucleoside **702** through the intermediates shown in Scheme 187 (85CPB102).

B. 1,2,4-TRIAZOLE HOMO *C*-NUCLEOSIDES

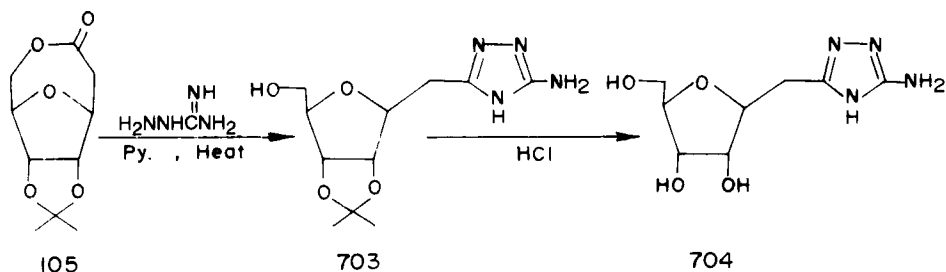
Condensation of the lactone (**105**) derived from 2,3-*O*-isopropylidene- β -D-ribofuranosyl acetic acid with aminoguanidine gave the 1,2,4-thiazole homo *C*-nucleoside **703** (75JA436; 81JOC3407) (Scheme 188).

C. 1,2,4-TRIAZOLE CARBOCYCLIC *C*-NUCLEOSIDES

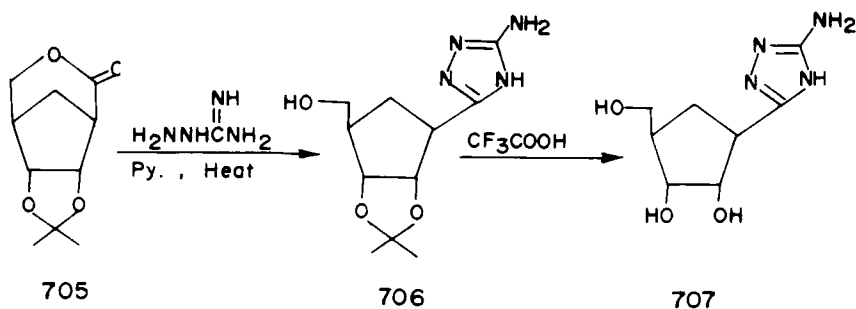
The only reported example of these analogs, **707**, was synthesized from the carbocyclic lactone derivative **705** and aminoguanidine (73TL1525; 76CJC861) (Scheme 189).



SCHEME 187



SCHEME 188

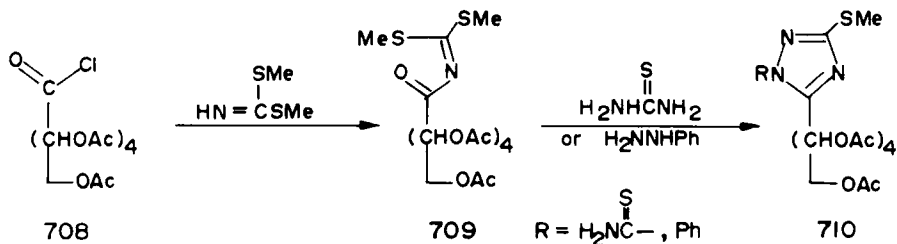


SCHEME 189

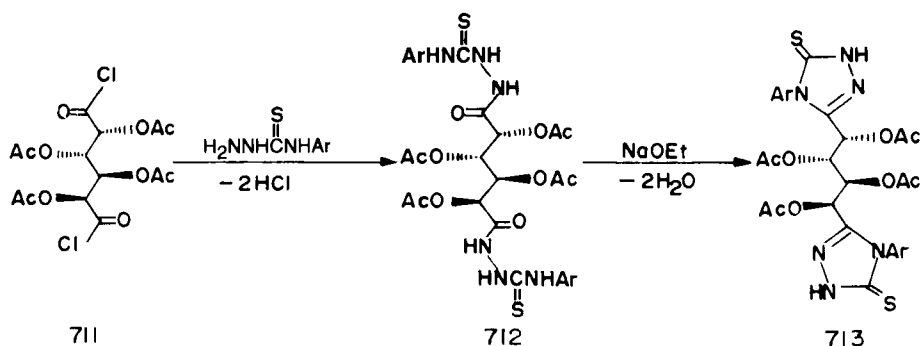
D. 1,2,4-TRIAZOLE ACYCLO C-NUCLEOSIDES

N-(Dimethylthio)methylene aldonic acid amides (**709**) reacted with thiosemicarbazide or phenylhydrazine to give the 3-(alditol-1-yl)-5-methylthio-1,2,4-triazoles **710** [86PHA551; 87GEP(D)245875] (Scheme 190).

The double-headed 1,2,4-triazole acyclo *C*-nucleosides **713** were obtained by cyclization of galactaroyl 1,4-bis(4-arylthiosemicarbazide) acetates (**712**)



SCHEME 190



SCHEME 191

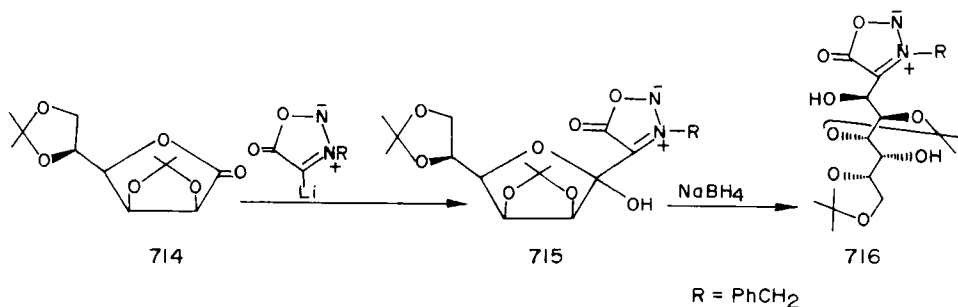
with sodium ethoxide (95MI3) (Scheme 191); the alternative cyclization to 2-arylamino-1,3,4-thiadiazoles (**777**) (Section XX,B) was performed under acidic conditions.

XV. 1,2,3-Oxadiazole C-Nucleosides

A. 1,2,3-OXADIAZOLE C-NUCLEOSIDES

1. 1,2,3-Oxadiazol-4-yl C-Nucleosides

A literature survey revealed a single report dealing with the synthesis of this class of C-nucleosides (74JOC1374). Reaction of 3-benzyl-4-lithio-1,2,3-oxadiazol-5-one with the L-gulonolactone derivative **714** stereospecifically afforded the 1,2,3-oxadiazol-4-yl C-nucleoside lactol **715**. Reduction of **715** with sodium borohydride gave the acyclo C-nucleoside **716** (Scheme 192).



SCHEME 192

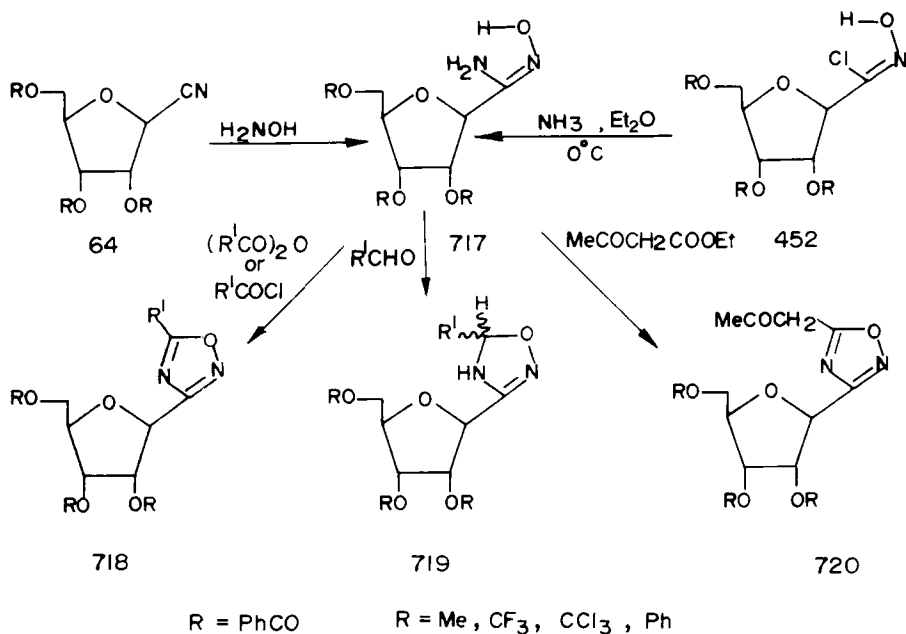
XVI. 1,2,4-Oxadiazole C-Nucleosides

A. 1,2,4-Oxadiazol-3-yl C-Nucleosides

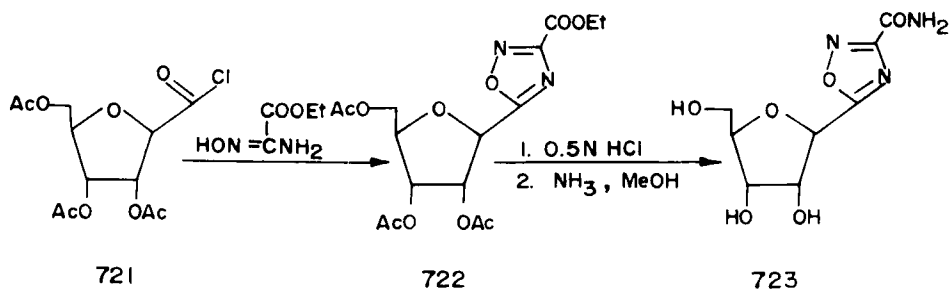
Reaction of the tri-*O*-benzoyl- β -D-ribofuranosylamidoxime **717** with acid anhydrides or acid chlorides (75JOC2481; 78MI15; 92MI3, 92MI4), aldehydes, and β -keto esters (75JOC2481) gave the 3-(β -D-ribofuranosyl)-1,2,4-oxadiazole C-nucleosides **718–720** (Scheme 193).

B. 1,2,4-Oxadiazol-5-yl C-Nucleosides

Reaction of the acid chloride **721** with ethoxycarbonylformamide oxime gave the 1,2,4-oxadiazol-5-yl C-nucleosides **722**, which was then transformed to the carboxamide **723** (Scheme 194). The latter showed some activity against L1210 and P388 leukemias in cell culture and antiviral activity against vaccinia and herpes simplex (HSV-2) with very little cellular activity (85JHC1747).



SCHEME 193

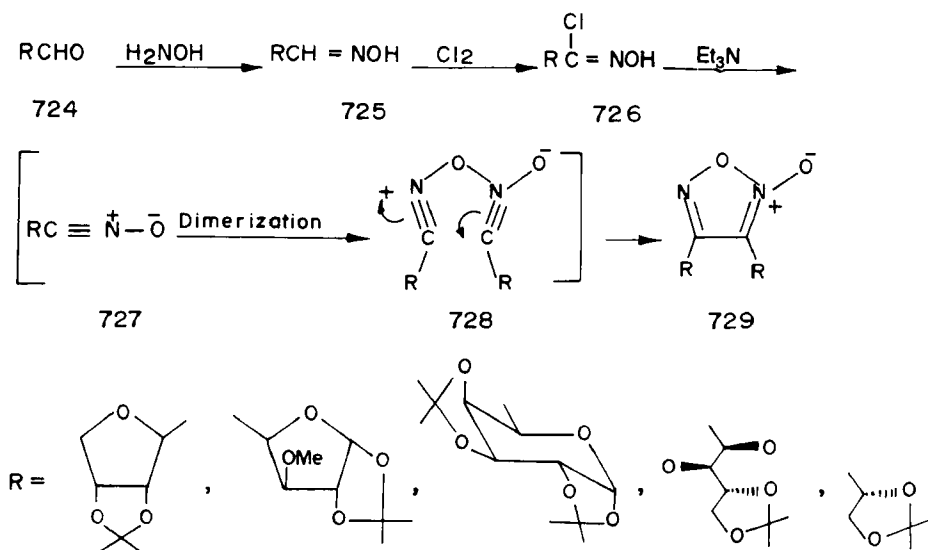


SCHEME 194

XVII. 1,2,5-Oxadiazole C-Nucleosides

A. 1,2,5-Oxadiazole C-NUCLEOSIDES AND THEIR REVERSE AND ACYCLO ANALOGS

The synthesis of 3,4-diglycosyl-1,2,5-oxadiazoles, their reverse and acyclo analogs (**729**) involves treatment of the corresponding hydroxamic acid halides **726** with triethylamine (71HCA921; 73MI6; 74MI4; 92T8053) (Scheme 195).



SCHEME 195

XVIII. 1,3,4-Oxadiazole C-Nucleosides

A. 1,3,4-OXADIAZOLE C-NUCLEOSIDES

These compounds were mainly synthesized by the reaction of tetrazole C-nucleosides (Section XXII,A) such as **730** with acid anhydrides or acid chlorides; the intermediate *N*-acyltetrazoles **731** were converted to **733** through the elimination of nitrogen [78KGS893; 81ACH(106)61; 84-ACH(115)319; 94MI11] (Scheme 196).

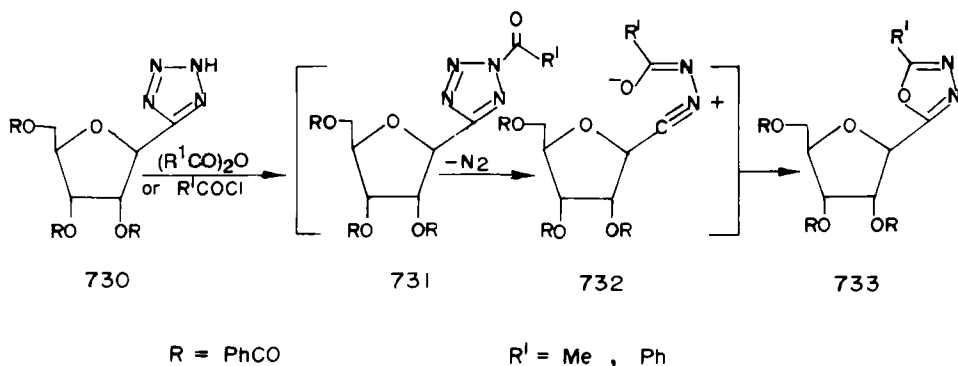
Dehydrative cyclization of the 1-aldonoylsemicarbazide **734** gave the 2-amino-1,3,4-oxadiazol-5-yl C-nucleoside **735**. The thiosemicarbazide analog **736** of **734** was also cyclized to **735** by the action of lead(II) oxide (86CCC1311) (Scheme 197).

B. 1,3,4-OXADIAZOLE CARBOCYCLIC C-NUCLEOSIDES

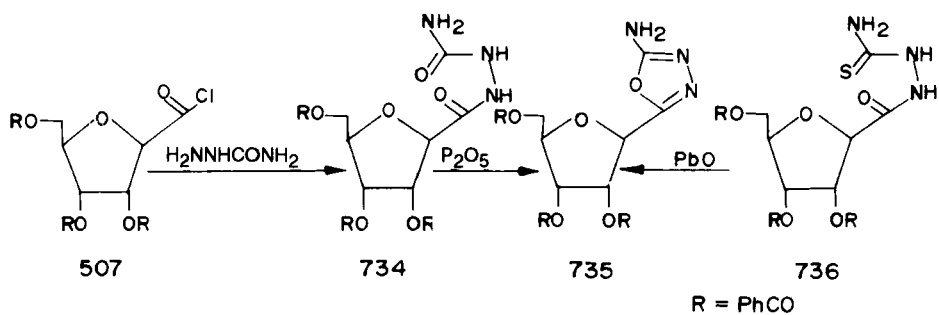
Oxidative cyclization of the semicarbazone **737** with lead tetraacetate gave the carbocyclic analog **738** of 1,3,4-oxadiazole C-nucleosides (75TL985; 76CJC861) (Scheme 198).

C. 1,3,4-OXADIAZOLE REVERSE C-NUCLEOSIDES

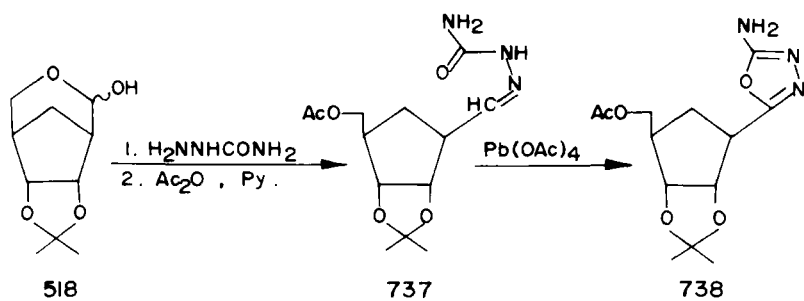
The reverse C-nucleoside **740** of this type was obtained either by oxidative cyclization of hydrazone **739** or by one-step reaction of the uronic acid derivative **741** with lithium benzoylaminophosphinimine (72HCA2816) (Scheme 199).



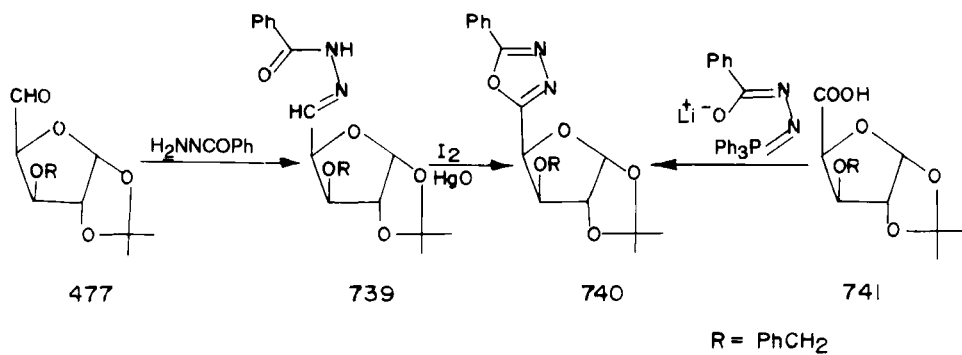
SCHEME 196



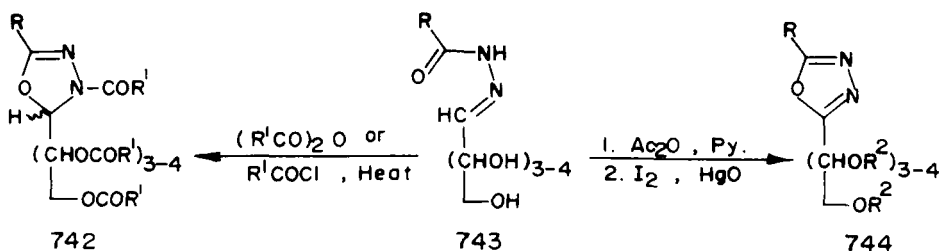
SCHEME 197



SCHEME 198



SCHEME 199

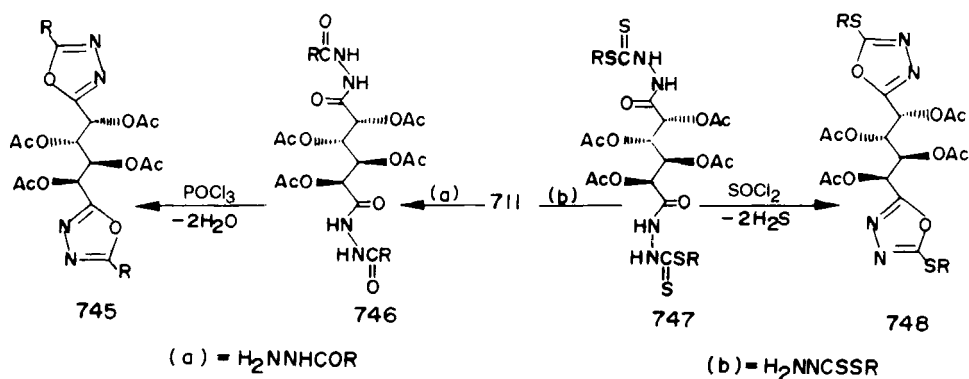


SCHEME 200

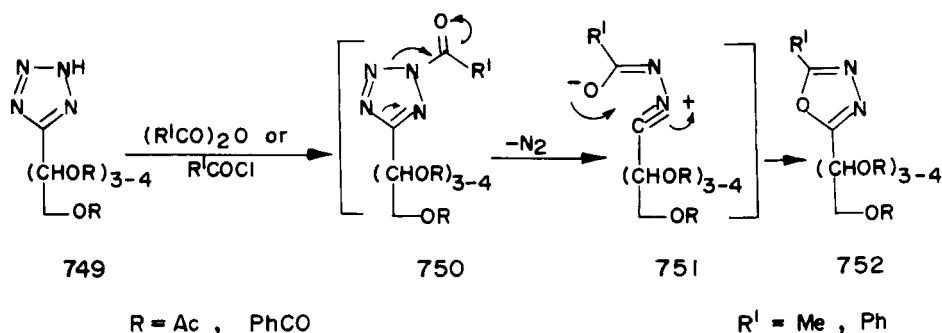
D. 1,3,4-Oxadiazole Acyclo C-NUCLEOSIDES

Monosaccharide acylhydrazones (**743**) and their acetates are the most commonly used starting materials for the synthesis of these analogs. While these hydrazones were condensatively cyclized with acid anhydrides or acid chlorides to 1,3,4-oxadiazoline acyclo C-nucleosides (**742**) (78MI10; 79MI11, 79MI12, 79MI15), their acetates were oxidatively cyclized with iodine and yellow mercury(II) oxide to 1,3,4-oxadiazole acyclo C-nucleosides (**744**) (70MI9; 72MI8; 76OPP107; 83OPP329) (Scheme 200).

Tetra-*O*-acetyl galactaroyl-1,4-bis(acylhydrazides) (**746**) were cyclized to the double-headed 1,3,4-oxadiazole acyclo C-nucleosides **745** by the action of dehydrating agents (74MI3; 76OPP113; 80MI8; 83MI7). The dithiocarbohydrazides **747** were also cyclized to **748** by the action of thionyl chloride (91JPR339, 91MI17) (Scheme 201).



SCHEME 201



SCHEME 202

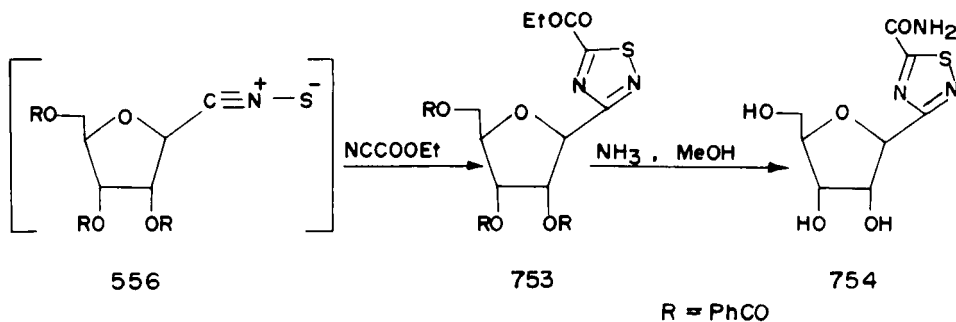
The tetrazole acyclo *C*-nucleoside **749** (Section XXII,C) afforded the 1,3,4-oxadiazole acyclo analogs **752** upon treatment with acid anhydrides or acid chlorides (76MI12; 91MI14; 92MI1; 94AQ130) (Scheme 202).

XIX. 1,2,4-Thiadiazole *C*-Nucleosides

A. 1,2,4-THIADIAZOLE *C*-NUCLEOSIDES

1. 1,2,4-Thiadiazol-3-yl *C*-Nucleosides

Reaction of the 2,5-anhydro-D-allononitrile *N*-sulfide **556** with ethyl cyanoformate gave **753**, which was de-*O*-benzoylated and amidated to **754** (84JOC2165; 91MI21) (Scheme 203). Compound **754** was inactive against some viruses and leukemia cells (84JOC2165).



SCHEME 203

XX. 1,3,4-Thiadiazole C-Nucleosides

A. 1,3,4-THIA DIAZOLE C-NUCLEOSIDES

Condensation of 1-phenyl-2-(thio-D-talonoyl)hydrazine (**756**) with benzaldehyde gave the 2-(α -D-lyxofuranosyl)-4,5-diphenyl-4,5-dihydro-1,3,4-thiadiazole **757** (78MI9) (Scheme 204).

Dehydrative heterocyclization of the 1-(2,5-anhydro-allonoyl)thiosemicarbazide derivative **736** followed by de-*O*-benzoylation furnished **759**, which inhibited the growth of *Escherichia coli* B (86CCC1311) (Scheme 205).

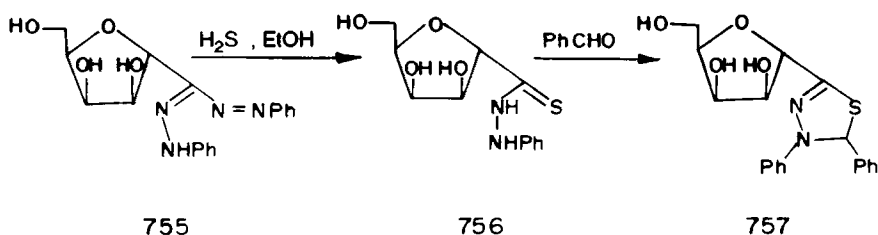
The acyclic analog **760** (Section XX,B) was converted to **761** by cyclization of its alditolyl chain (94MI10) (Scheme 206).

B. 1,3,4-THIA DIAZOLE ACYCLO C-NUCLEOSIDES

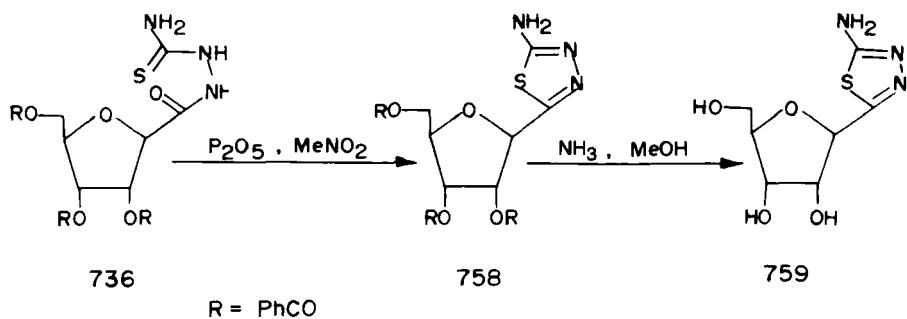
1-Phenyl-2-thioaldonoylhydrazines **763**, obtained from the *aldehydo*-sugar *N,N'*-diphenylformazans **762**, condensed with benzaldehyde to provide the 1,3,4-thiadiazoline acyclo C-nucleosides **764** (53CB697) (Scheme 207).

The isomeric C-nucleosides **766** were also prepared by the same reaction; the functionalities of the two reacting species, however, were interchanged (54AK517) (Scheme 208).

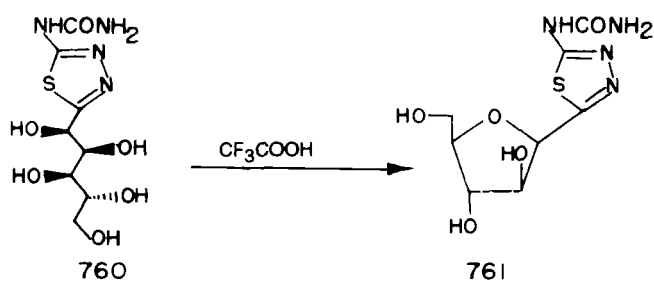
Whereas *aldehydo*-sugar thiobenzoylhydrazones (54AK513) and thiosemicarbazones (**768**) (86JPR1; 87BC3405) were dehydrogenatively cyclized with iron(III) chloride to the 1,3,4-thiadiazole acyclo C-nucleosides **767**, heating of **768** with acid anhydrides or acid chlorides affected heterocyclization to the 1,3,4-thiadiazoline C-nucleosides **769** (79MI15; 87BCJ-3405) (Scheme 209).



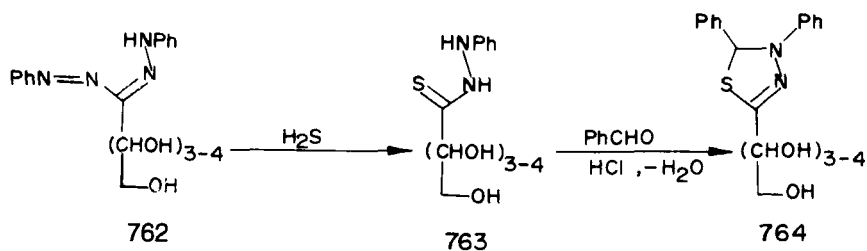
SCHEME 204



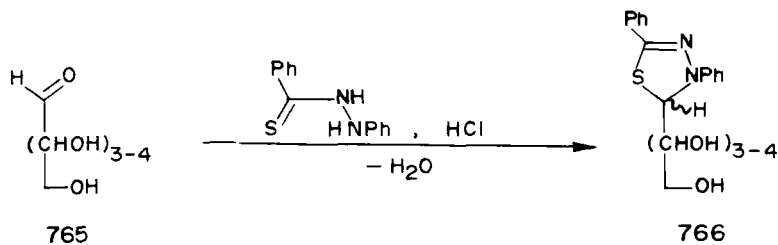
SCHEME 205



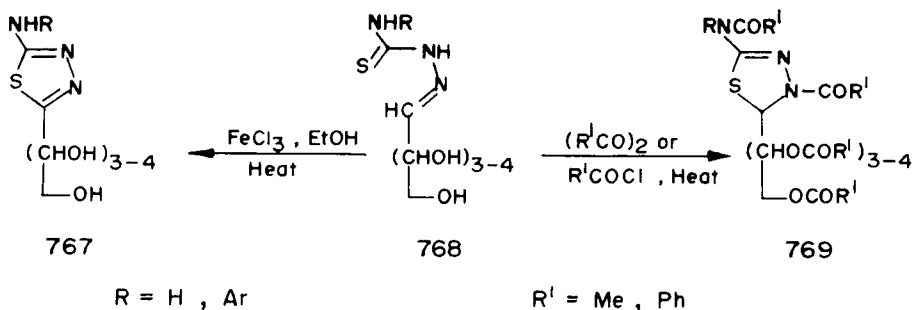
SCHEME 206



SCHEME 207



SCHEME 208

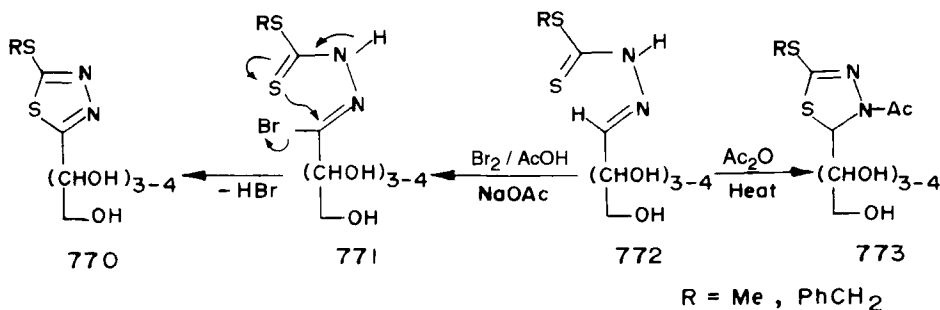


SCHEME 209

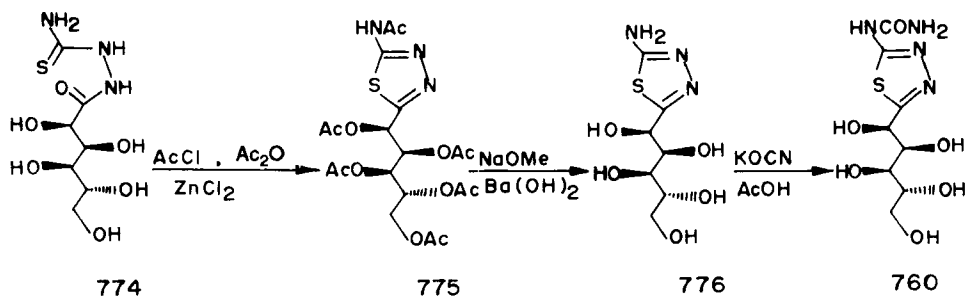
Oxidative cyclization of *aldehydo*-sugar *S*-alkylhydrazoncarbodithioates (**772**) with bromine in acetic acid and anhydrous sodium acetate gave the corresponding 2-(alditol-1-yl)-5-alkylthio-1,3,4-thiadiazoles **770**. In addition, cyclocondensation of **772** by heating with acetic anhydride gave the 1,3,4-thiadiazoline *C*-nucleosides **773** (97UP1) (Scheme 210).

1-D-Gluconoylthiosemicarbazide (**774**) underwent dehydrocyclization by heating with acetic anhydride and zinc chloride to the 2-acetamido-1,3,4-thiadiazole acyclo *C*-nucleoside **775**. The latter was deacetylated and transformed to the 5-ureido derivative **760** (94MI10) (Scheme 211).

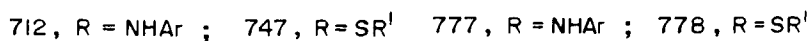
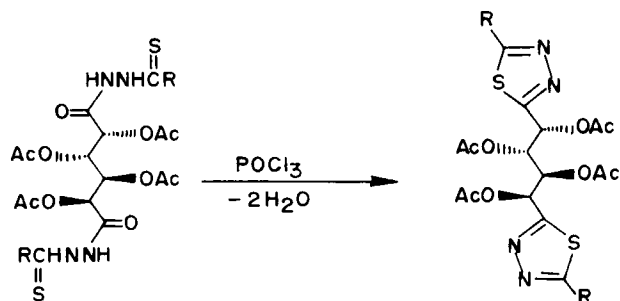
Dehydrocyclization of the previously mentioned tetra-*O*-acetyl-galactaric acid 1,4-bis(4-arylthiosemicarbazide) **712** by heating with phosphoryl chloride gave the double-headed 2-arylamino-1,3,4-thiadiazole acyclo *C*-nucleosides **777** (95MI3). Similar treatment of the tetraacetates of galactosyl 1,4-bis(dithiocarbohydrazides) **747** gave **778** (91JPR339, 91MI17) (Scheme 212).



SCHEME 210



SCHEME 211

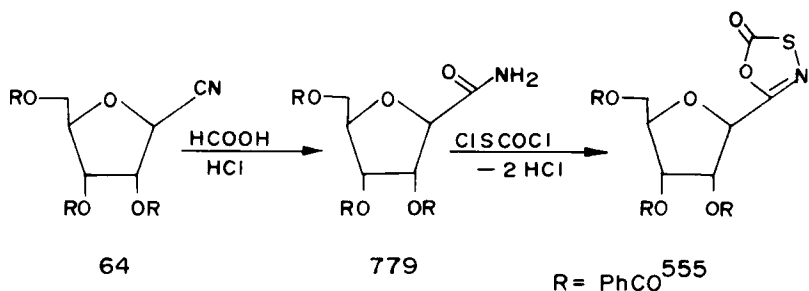


SCHEME 212

XXI. 1,3,4-Oxathiazole C-Nucleosides

A. 1,3,4-OXATHIAZOL-5-YL C-NUCLEOSIDES

The single example of this class that is known so far (**555**) has been synthesized as a stable precursor for the thermolytic *in situ* production of the allonoylnitrile *N*-sulfide **556**; the latter is the reactive species in the synthesis of isothiazole (Section XI; Scheme 149) and 1,2,4-thiadiazole C-nucleosides (Section XIX; Scheme 203). The 5-(tri-*O*-benzoyl- β -D-ribofuranosyl)-1,3,4-oxathiazol-2-one (**780**) was obtained from the 2,5-anhydro-D-allonic acid amide **779** by heating with chlorocarbonylsulfenyl chloride (84JOC2165; 91MI21) (Scheme 213).



SCHEME 213

XXII. Tetrazole C-Nucleosides

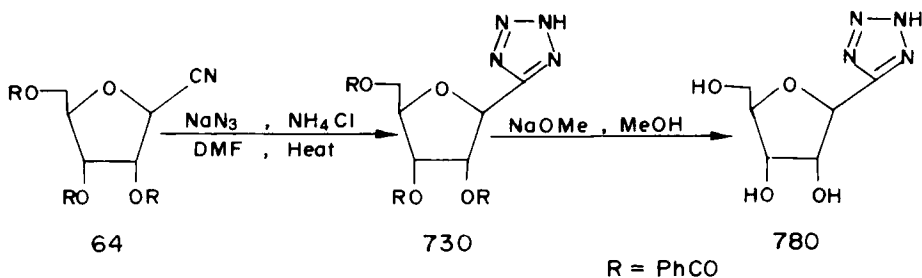
A. TETRAZOLE C-NUCLEOSIDES

The method of choice for the preparation of these compounds, for example, **730**, is the reaction of glycosyl cyanides such as **64** with ammonium azide [77MI7; 78KGS893, 78MI5; 81ACH(106)61; 92JCS(P1)2593; 94MI11] (Scheme 214).

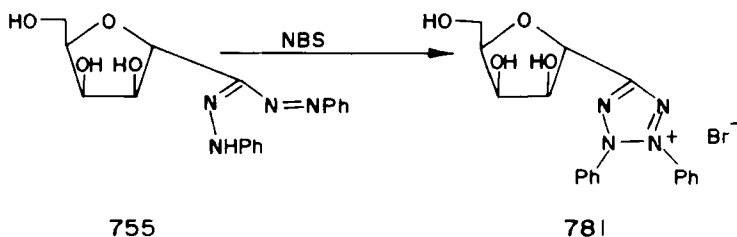
Cyclization of the *N,N'*-diphenylformazans **755** with *N*-bromosuccinimide (NBS) gave the tetrazolium *C*-nucleoside bromide **781**, a reaction that can be reversed by reduction with L-ascorbic acid (vitamin C) (78MI9) (Scheme 215).

B. TETRAZOLE CARBOCYCLIC C-NUCLEOSIDES

Similar to the preparation of the parent tetrazole *C*-nucleosides, the carbocyclic analog **784** was prepared from the carbocyclic nitrile derivative **782** and lithium azide (93MI12) (Scheme 216).



SCHEME 214



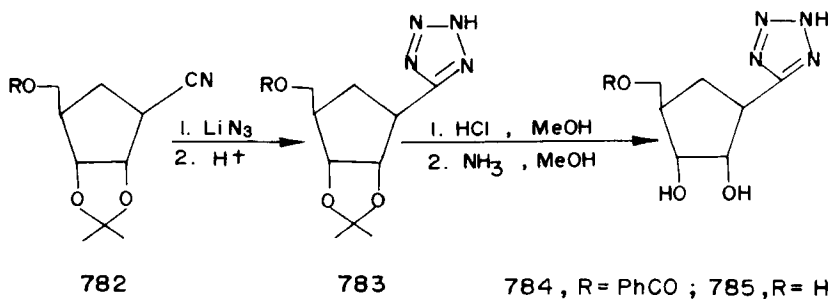
SCHEME 215

C. TETRAZOLE ACYCLO C-NUCLEOSIDES

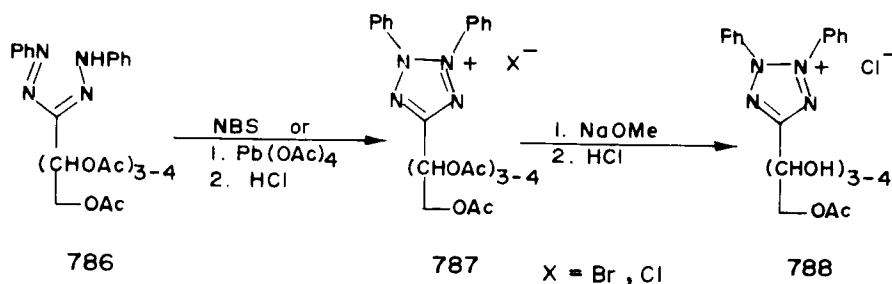
Poly-*O*-acetyl *aldehyde*-sugar *N,N'*-diphenylformazans (**786**) are easily accessible starting materials and readily cyclizable with $\text{Pb}(\text{OAc})_4$ (53CB472, 53MI2) or NBS (57JCS3802; 88MI7) to 5-(alditol-1-yl)-2,5-diphenyltetrazolium salts (**787**) (Scheme 217).

Cycloaddition of hydrazoic acid to aldonitriles (**618**) (71MI2; 75MI5; 79MI13; 90MI3) or thermolysis of the 1,1-diazo acyclic sugar derivatives **789** [95JCS(P1)1747] yielded the tetrazole acyclo *C*-nucleosides **749** (Scheme 218).

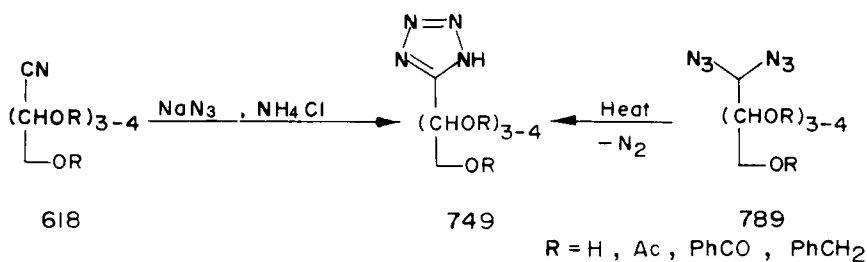
The relation between the configuration of the alditolyl chains of **749** and their conformations has been thoroughly studied using ^1H NMR spectrometry (75MI4; 84MI1; 87MI5). The chains of **749** were found to occupy extended planar zigzag or bent (sickle) conformations, whichever contained less unfavorable 1,3-eclipsed interactions of the polar groups attached to the alditolyl chains.



SCHEME 216



SCHEME 217



SCHEME 218

XXIII. Azine C-Nucleosides

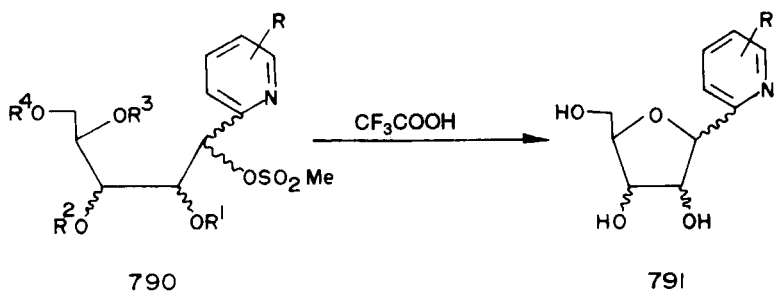
A. PYRIDINE C-NUCLEOSIDES

1. 2(6)-Pyridyl C-Nucleosides

Acid-catalyzed cyclization of 2-(2-methylsulfonyloxypentitol-1-yl)pyridines (Section XXIII,A,1) carrying acid labile *O*-protective groups, such as **790**, is one of the most frequently used methods for the preparation of these compounds, probably because of the ease of formation of the starting compounds (**790**). A mixture of varying proportions of the two anomeric C-nucleosides (**791**) is usually obtained (86MI8; 88CPB634; 91MI24, 91MI25; 92HCA1613; 93JHC1245, 93JMC1859; 94CL265) (Scheme 219).

Cyclization of *O*-benzylated 2-pyridyl acyclo C-nucleoside using diethyl azodicarboxylate and triphenylphosphine to pyridyl C-nucleosides has been reported [95JAP(K)95/118268].

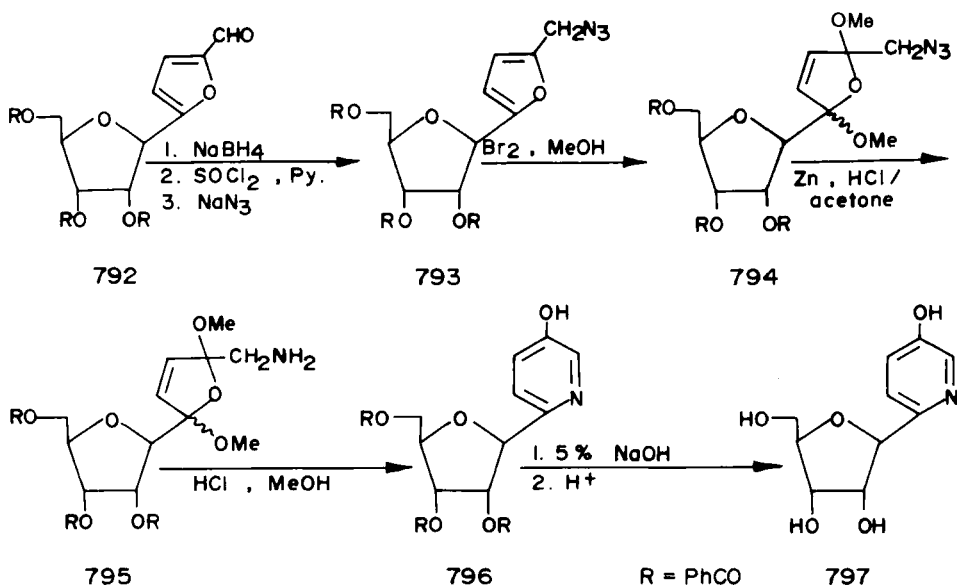
Maeba *et al.* prepared the 5-hydroxy-2-(β -D-ribofuranosyl)pyridine **797** through dihydrofurfurylamine ring transformation of **795** (88JHC503) (Scheme 220).



R = H, Me, CONH₂, COCH₂NH₂, COOMe, Br
 R¹, R², R³, R⁴, = acid labile groups

SCHEME 219

Recently, C-nucleoside synthesis by glycosyl free radical coupling with protonated nitrogen heterocycles started to gain impetus. Thus, photoirradiation of the 1-(2,5-anhydro-D-allonoyloxy)pyridine-2-thione derivative **798** gave the D-ribofuranosyl free radical **799** that couples with substituted pyridines to give a mixture of the two anomers of 2-pyridyl C-nucleosides



SCHEME 220

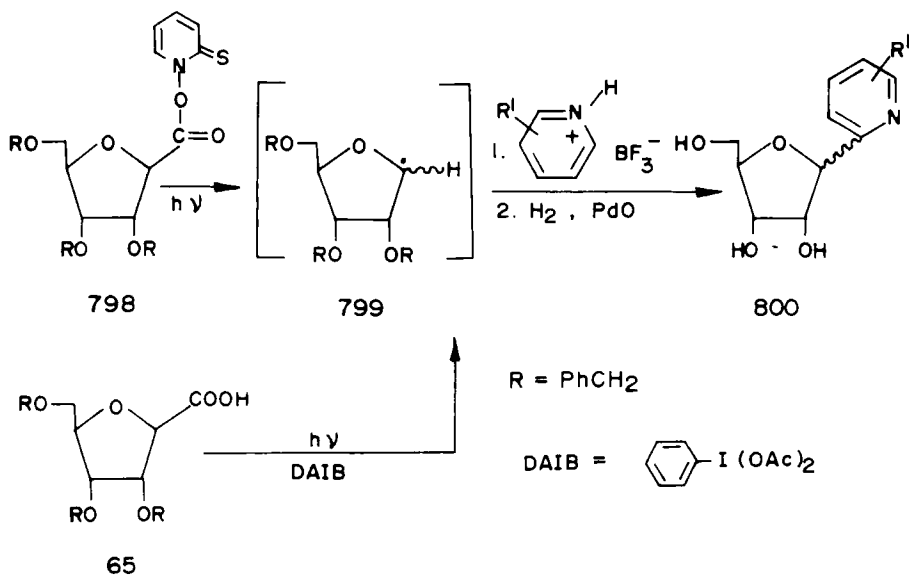
800 [91TL3377; 94JCS(P1)2407, 94JCS(P1)2931]. Alternatively, radical C-glycosylation of protonated pyridine derivatives has also been accomplished by decarboxylative photolysis of aldonic acid derivatives such as **65** in the presence of hypervalent iodine compounds such as (diacetoxyiodo)benzene (DAIB), or bis(trifluoroacetoxy)iodo]benzene [91TL6559; 92TL7575; 93-JAP(K)93/306283, 93JCS(P1)2417] (Scheme 221).

The 1,2-diazine system of the 1,2,4-triazine C-nucleoside **801** (Section XXX,A,1) is activated by the electron-withdrawing effect of the two trifluoromethyl groups. Consequently, it undergoes inverse [4 + 2] cycloaddition with electron-rich vinyl compounds as dienophiles, affording adducts that lose nitrogen to furnish 2-pyridyl C-nucleosides such as **802** (95AP175) (Scheme 222).

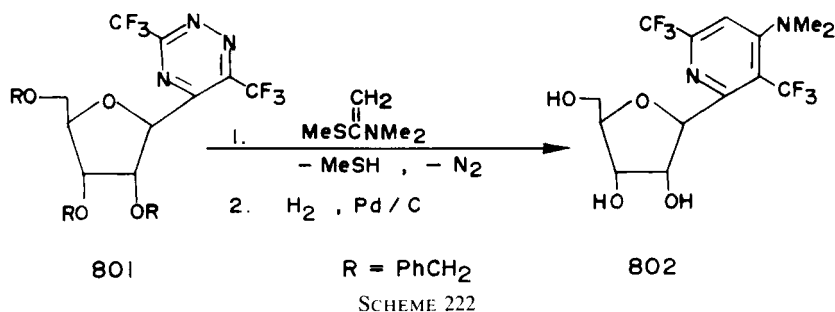
Only 2-carbamoyl-6-(β -D-ribofuranosyl)pyridine (88CPB634) and its 4-carbamoyl congener (91MI25) revealed weak to moderate antitumor activity; the many other differently substituted 2-pyridyl C-nucleosides were inactive as antitumor and antiviral agents (86MI8; 92HCA1613; 93-JHC1245).

2. 3(5)-Pyridyl C-Nucleosides

Similar to their 2-pyridyl analogs, 3-pyridyl C-nucleosides (**804**) were prepared by acid-catalyzed cyclization of 3-(2-methylsulfonyloxypentitol-



SCHEME 221



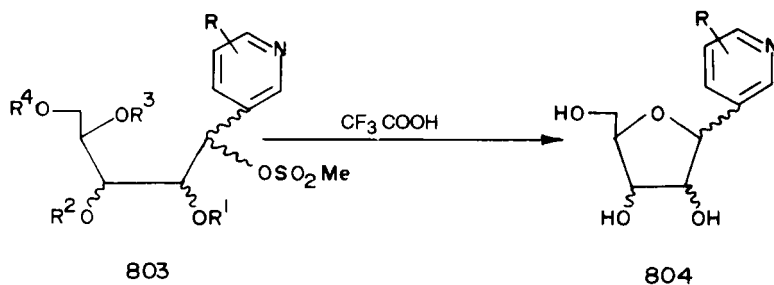
1-yl)pyridines carrying acid-sensitive *O*-protective groups (**803**) [67JMC320; 69MI4; 70LA(736)68; 73AGE139; 87JMC924, 87MI7; 88JCS(P1)545, 88JOC3473, 88MI15, 88MI16; 89MI11; 91HCA397, 91MI27, 91T3297; 94MI8] (Scheme 223).

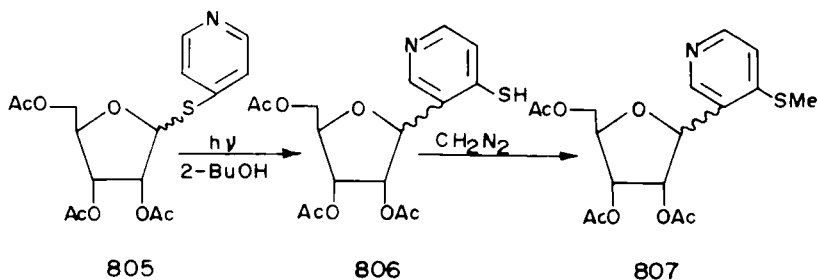
Photorearrangement of the anomeric pair of 4-pyridyl thioglycosides **805** followed by *S*-methylation gave the two anomers of **807** in low yield (5%) (79JOC1892) (Scheme 224).

The 3-(*D*-ribofuranosyl)glutarimide derivatives **809**, homoheterocyclic analogs of showdomycin (**4**), were synthesized by Wittig reaction of glutarimide phosphoranes with **67** (Scheme 225) and found to be slightly active against *Varicella zoster* virus (88MI14; 90TL907).

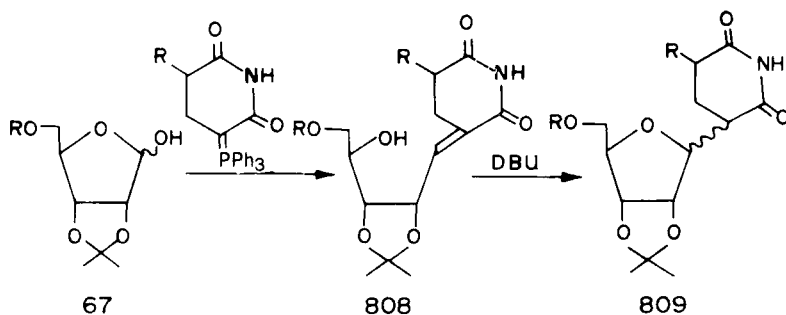
An alternative route for 3-glycosylglutarimides has been reported, according to which the 5-(*β*-*D*-glucopyranosyl)barbiturate derivative **810** underwent unusually facile barbiturate ring cleavage with alkali losing the C2 carbonyl to yield, after acetylation, the 3-(*β*-*D*-glucopyranosyl)glutarimide derivative **812** (95MI5) (Scheme 226).

Palladium-mediated C—C bond formation between the glycal derivative **813** and 3-iodopyridines (e.g., **814**) generated solely the *β*-linked 3-pyridyl





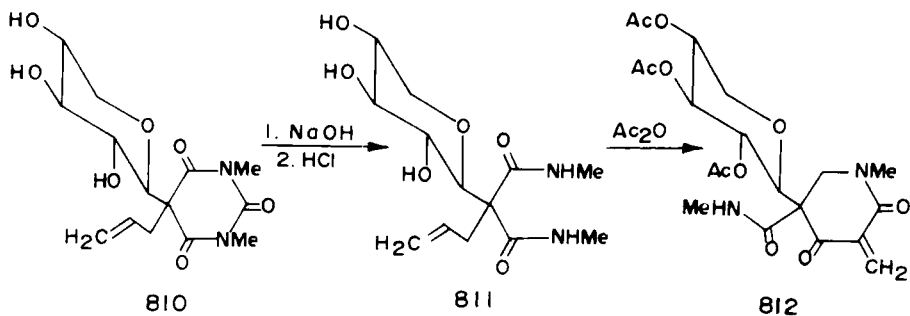
SCHEME 224



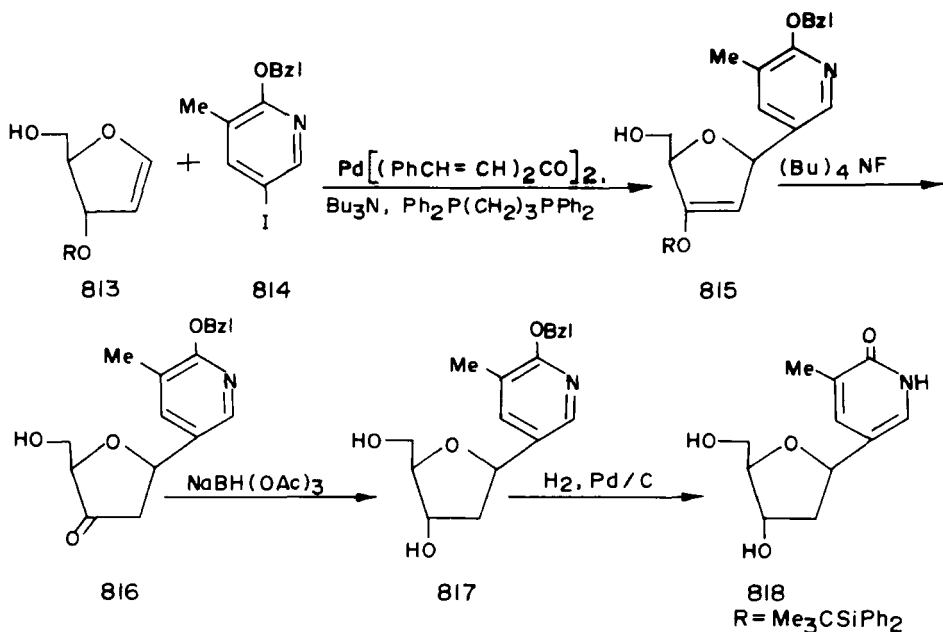
SCHEME 225

unsaturated C-nucleoside **815**, which was reduced and de-O-protected to give **818** (95JOC5356) (Scheme 227).

3-Carbamoyl-5-(β -D-ribofuranosyl)pyridine showed some antitumor activity (87JMC924). Many other 3-pyridyl C-nucleosides, however, were inactive as inhibitors of thymidylate synthetase or dihydrofolate reductase



SCHEME 226



SCHEME 227

(67JMC320), or as antibacterial [70LA(736)68], antiviral [70LA(736)68; 88MI16; 91MI27; 94MI8], or antitumor agents [70LA(736)68; 87MI7; 88JCS(P1)545, 88MI16; 89MI11; 91MI27; 94MI8]. The conformations of some 3-pyridyl C-nucleosides have been studied [95SA(A)153].

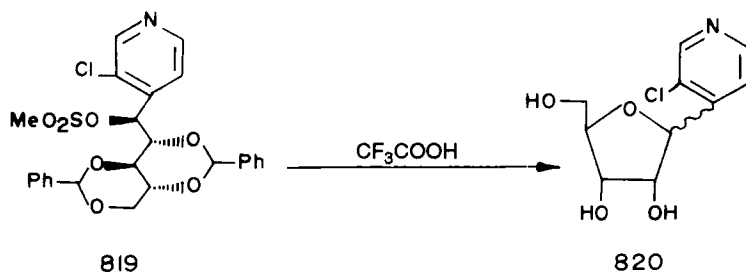
3. 4-Pyridyl C-Nucleosides

The anomeric pair of 3-chloro-4-(D-ribofuranosyl)pyridine (**820**) was obtained by acid-catalyzed cyclization of the corresponding acyclo derivative **819** (Scheme 228). The anomeric mixture **820** was neither cytostatically nor antivirally active (89MI11).

B. PYRIDINE HOMO C-NUCLEOSIDES

1. 2(6)-Pyridyl Homo C-Nucleosides

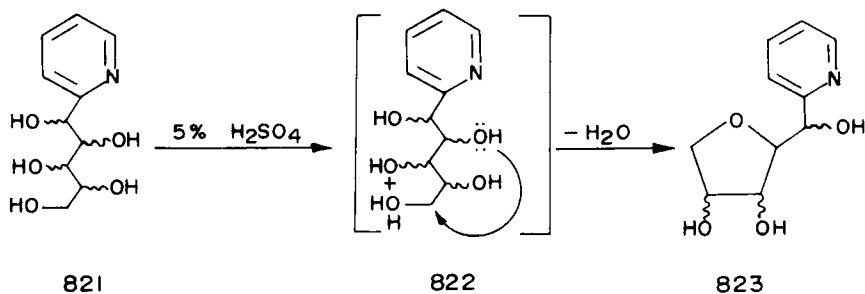
Only 2-pyridyl homo C-nucleosides were reported. Dehydrative cyclization of the unprotected 2-(pentitol-1-yl)-pyridines **821** by heating with 5% sulfuric acid was claimed to take place via $\text{S}_{\text{N}}2$ displacement of the



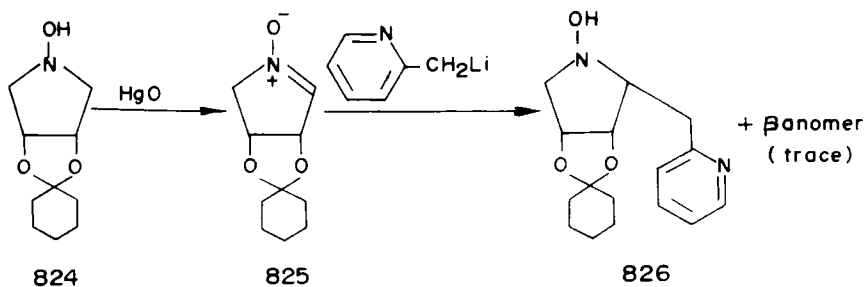
SCHEME 228

protonated HO-5' by O-2' to give the corresponding 2-pyridyl homo C-nucleoside **823** (87MI6; 88MI12) (Scheme 229).

Tronchet *et al.* synthesized the 2-pyridyl homo C-nucleoside analog **826** having a nitrogen-containing sugar moiety by reacting the *DL*-threo-1-pyrroline derivative **825** with pyrid-2-ylmethyllithium (95MI2) (Scheme 230).



SCHEME 229



SCHEME 230

C. PYRIDINE CARBOCYCLIC C-NUCLEOSIDES

1. 2(6)-Pyridyl Carbocyclic C-Nucleosides

Photoirradiation of the 2-thiopyridine-1-(2,3-benzoyloxycyclobutanoate) (**827**) generated the 2,3-benzoyloxycyclobutane free radical **828**, which coupled with 3-substituted pyridinium trifluoroacetates to give the 2-pyridyl carbocyclic C-nucleosides (**829**) [94JCS(P1)2407] (Scheme 231).

D. PYRIDINE REVERSE C-NUCLEOSIDES

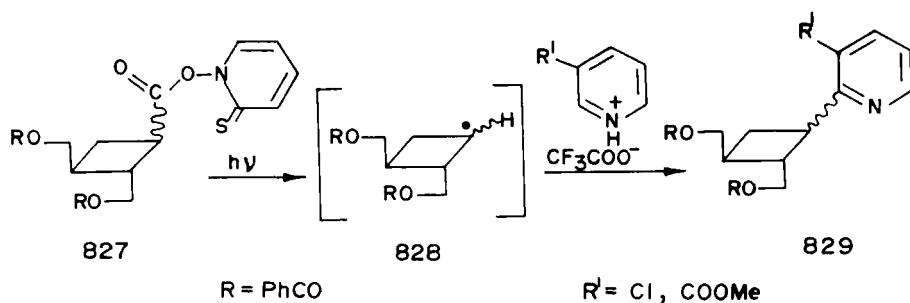
1. 2(6)-Pyridyl Reverse C-Nucleosides

Only 2-pyridyl reverse C-nucleosides are known. Coupling saccharide free radicals **831** and **834** with protonated pyridine derivatives gave the 2-pyridyl reverse C-nucleosides **832** and **835**, respectively. Free radical **831** was obtained by decarboxylative photolysis of the uronic acid derivative **830** in the presence of hypervalent iodine compounds (92TL7575) (Scheme 232), whereas free radical **834** was obtained by thermal homolysis of the carbon-iodine bond in the 6-iodo-6-deoxy-D-galactopyranose derivative **833** in the presence of benzoyl peroxide (93JOC959) (Scheme 233).

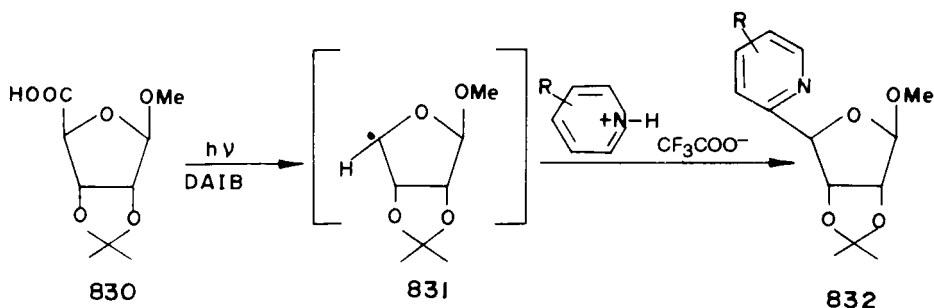
E. PYRIDINE ACYCLO C-NUCLEOSIDES

1. 2(6)-Pyridyl Acyclo C-Nucleosides

Reaction of 2-lithiopyridines with properly protected *aldehydo*-sugar derivatives such as **226** is a very valuable route for the synthesis of this class



SCHEME 231



DIAB = (diacetoxyiodobenzene)

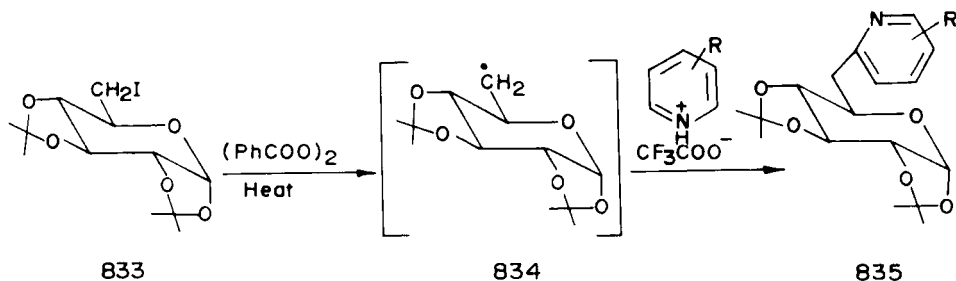
SCHEME 232

of C-nucleosides; a mixture of the anomeric pair **836** is obtained [85MI11; 86MI8; 88CPB634; 91MI24, 91MI25; 92HCA1613; 94CL265; 95JAP(K)95/118268, 95S638] (Scheme 234). 2-Trimethylsilylpyridine has also been used in place of 2-lithiopyridine [77JAP(K)77/48693].

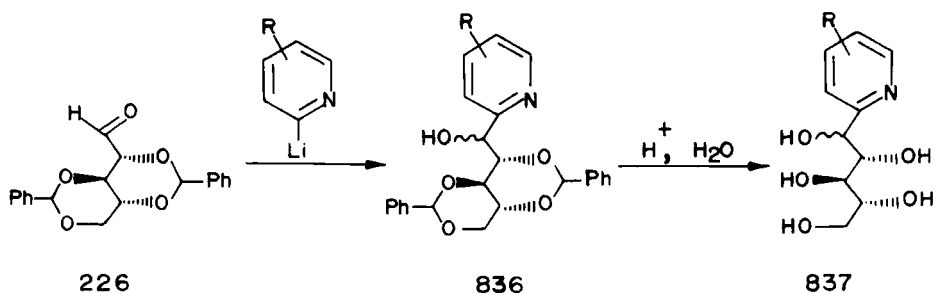
Akin to the aforementioned synthesis is the reaction of 2-lithiopyridines with derivatives of aldono-lactone such as **838**, which usually took place stereospecifically to give one of the two possible hemiacetal (lactol) C-nucleosides **839**. Reduction of the latter gave a mixture of the two possible stereoisomers **840** (74JOC1374; 88CPB634, 88MI15) (Scheme 235).

The 1,2-di-(*D-arabino*-tetritol-1-yl)pyridin-4-one C-nucleoside **842** was reported to be formed, among other products, when 1-amino-1-deoxy-*D*-fructose (**239**) reacted with malondialdehyde (92MI6) (Scheme 236).

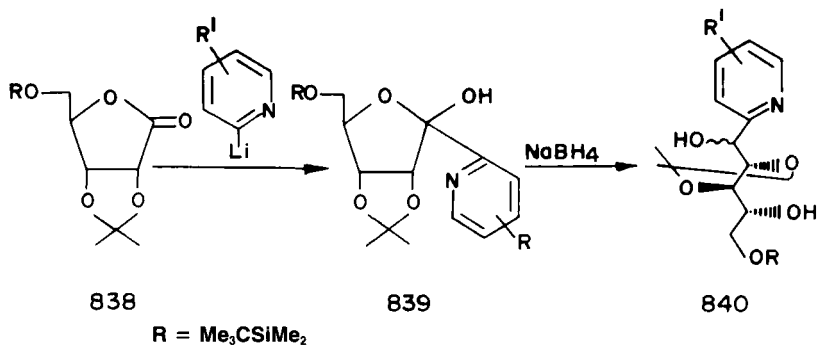
Formation of the pyridine nucleus of the nucleoside **844** was effected by cobalt-catalyzed co-cyclotrimerization of the L-threononitrile derivative **843** with acetylene (94TA299) (Scheme 237).



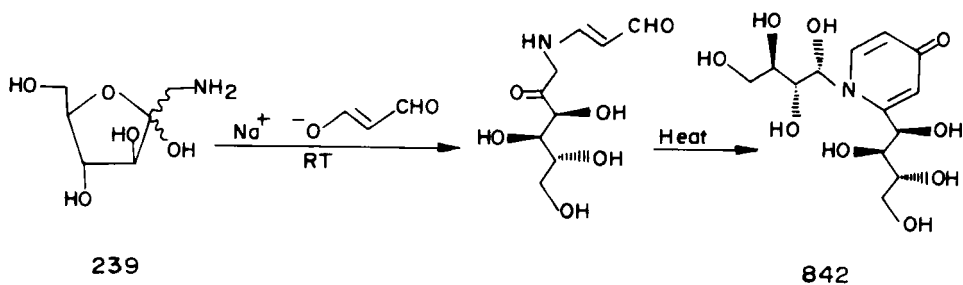
SCHEME 233



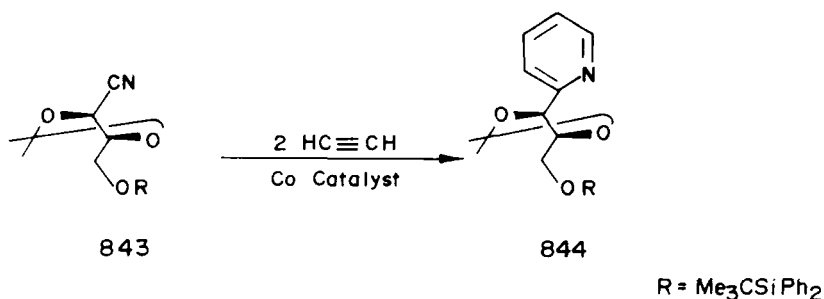
SCHEME 234



SCHEME 235



SCHEME 236



SCHEME 237

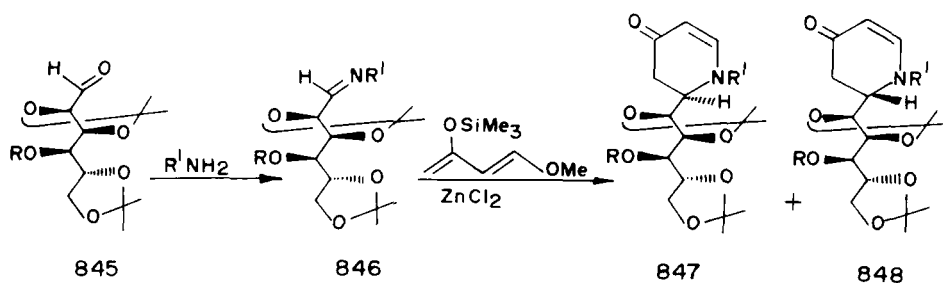
The two diastereoisomeric piperidone acyclo *C*-nucleosides **847** and **848** were formed by [4 + 2] cycloaddition of the sugar azomethine derivative **846** to 2-trimethylsilyloxy-4-methoxy-1,3-butadiene (95T2969) (Scheme 238).

Transformation of the bromo function of 2-bromo-2-(alditol-1-yl)pyridine to carbamoyl (93JMC1859) and carbamoylmethyl (93JHC1245) functions has been reported.

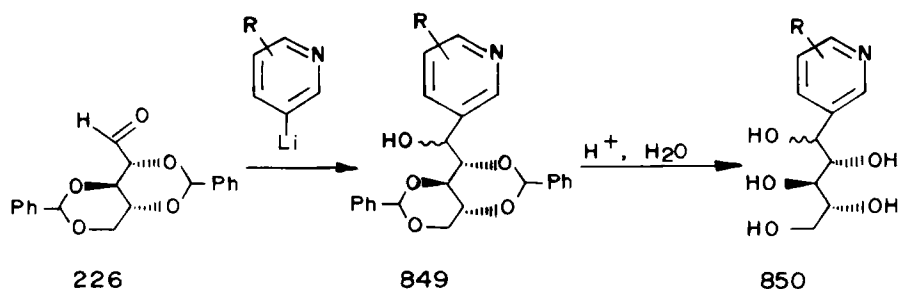
2. 3(5)-Pyridyl Acyclo *C*-Nucleosides

Many pyrid-3-yl *C*-nucleosides (e.g., **850** and **852**) were prepared by reaction of 3-lithiopyridines with *aldehydo*-sugar derivatives (e.g., **226**) [70LA(736)68; 73AGE139; 87JMC924, 87MI7; 88JCS(P1)545, 88MI16; 91MI27, 91TL3297; 94MI8] (Scheme 239) or aldonolactone derivatives (e.g., **838**) followed by reduction of **851** (88JOC3473, 88MI15; 91HCA397) (Scheme 240).

Condensation of glutarimide phosphoranes with the *aldehydo*-sugar derivative **226** gave a mixture of the *E*- and *Z*-isomers of **853** (88S325) (Scheme 241).



SCHEME 238



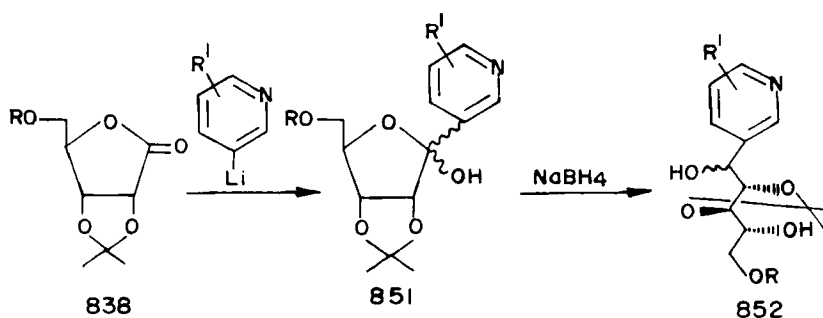
SCHEME 239

The 3-pyridyl acyclo C-nucleosides **857** bearing truncated sugar residues were prepared by condensation of derivatives of ethylene glycol such as **854** with 3-halomethylpyridines (**855**) in the presence of sodium hydride (91T10065; 93T4085; 94MI12) (Scheme 242).

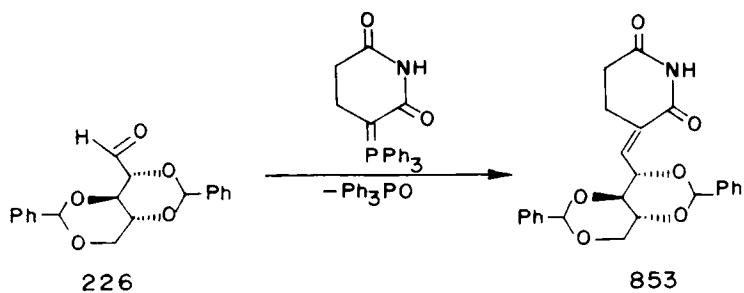
3. 4-Pyridyl Acyclo C-Nucleosides

Reaction of 2,4:3,5-di-O-benzylidene- α -D-ribose (**226**) with 3-chloro-4-lithiopyridine gave a mixture of the two isomeric 4-pyridyl acyclo C-nucleosides **858** (89MI11) (Scheme 243).

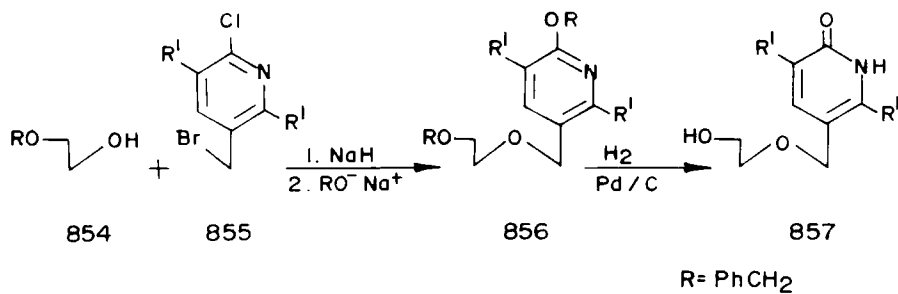
The glutarimide C-nucleoside **860** was obtained by condensation of the unsaturated aldonic acid esters **859** with *tert*-butyl carbamoylacetate. The deprotected compounds **861** were not active as anticandidal, antifungal, or antiviral agents. However, they showed antibacterial activity against *Mycobacterium intracellulare* (92CJC1662) (Scheme 244).



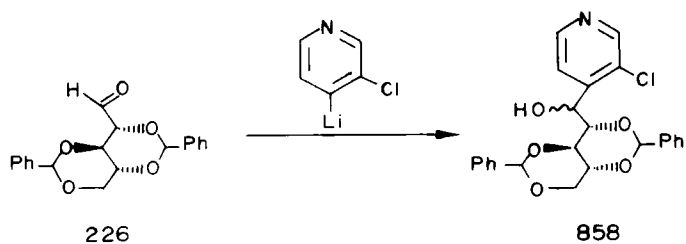
SCHEME 240



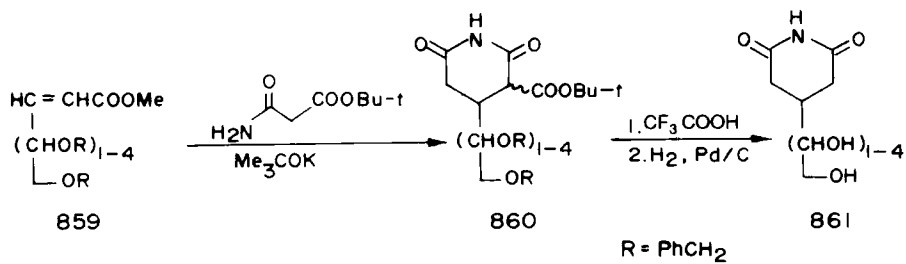
SCHEME 241



SCHEME 242



SCHEME 243



SCHEME 244

XXIV. 1,2-Diazine C-Nucleosides

A. PYRIDAZINE C-NUCLEOSIDES

1. 3(6)-Pyridazinyl C-Nucleosides

The 2-(β -D-glycofuranosyl)furan derivative **862** was photooxygenated followed by reduction with dimethyl sulfide to give the dicarbonyl compound **863** [84AQ(C)215, 84MI6; 86AQ(C)179], and **165** was methoxylated (83JOC2998) to **865** or oxidized followed by methylation to **868** (87-JOC4521). These compounds (**863**, **865**, and **868**) were cyclocondensed with hydrazine hydrate to the 3-(β -D-glucufuranosyl)pyridazines **864**, **866**, and **869**, respectively (Schemes 245 and 246). 2-(β -D-Glycofuranosyl)pyranone derivatives were also used to prepare 3-pyridazinyl C-nucleosides by similar reaction pathways [91JCS(P1)939].

The dihydropyridazinone C-nucleoside **871** was obtained by reaction of the 4-(β -D-glycofuranosyl)-4-oxobutyric acid **870** and then dehydrogenated and deprotected to **872** [90JCS(P1)73] (Scheme 247).

2. 4(5)-Pyridazinyl C-Nucleosides

Compounds **875** belonging to this class of C-nucleosides were synthesized by Diels–Alder cycloaddition with inverse electron demand of 3,6-disubstituted 1,2,4,5-tetrazines containing a highly reactive diazadiene system and β -D-ribofuranosylacetylenes (**305**) (94AP365) (Scheme 248).

B. PYRIDAZINE ACYCLO C-NUCLEOSIDES

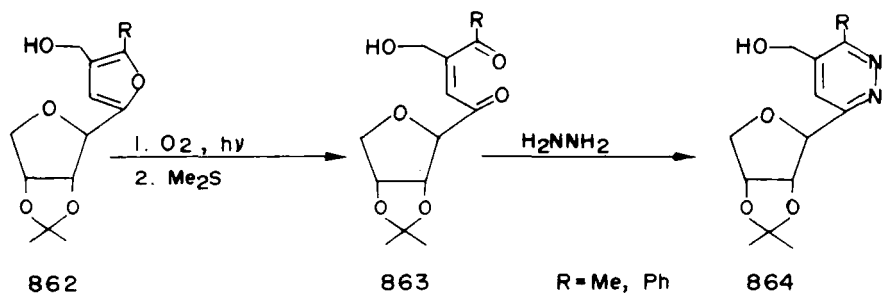
1. 3(6)-Pyridazinyl Acyclo C-Nucleosides

Removal of the *O*-protective groups of 3-hydrazono derivatives of aldehydo-sugars such as **876** culminated in intramolecular cyclization to afford 3-(alditol-1-yl)pyridazines (**879** and **880**) (70CB1846; 75JHC75) (Scheme 249).

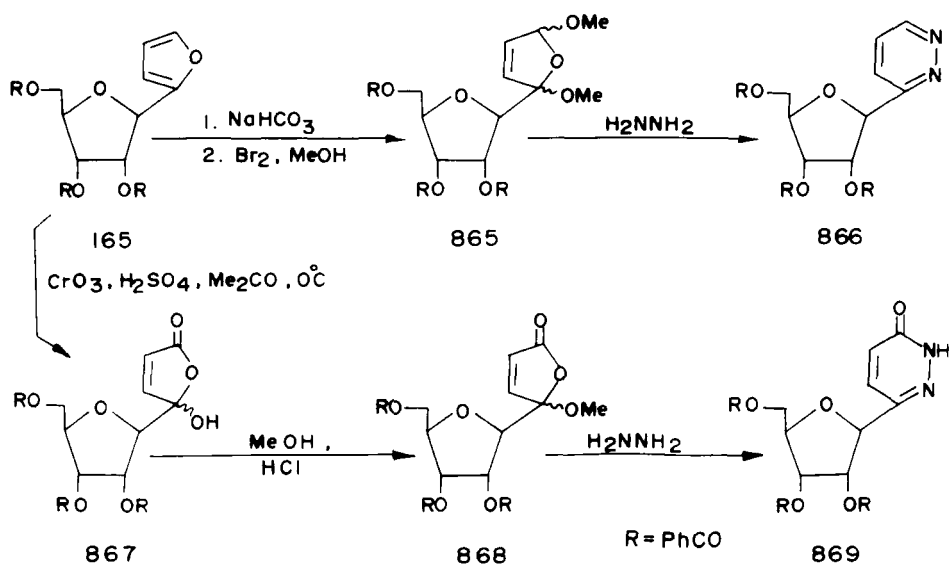
Photooxygenation of the 2-(alditol-1-yl)furan compound **881** and reduction of the produced unisolable peroxide gave the enedione **882**. Cyclization of **882** with hydrazine gave **883** (84MI6) (Scheme 250).

2. 4(5)-Pyridazinyl Acyclo C-Nucleosides

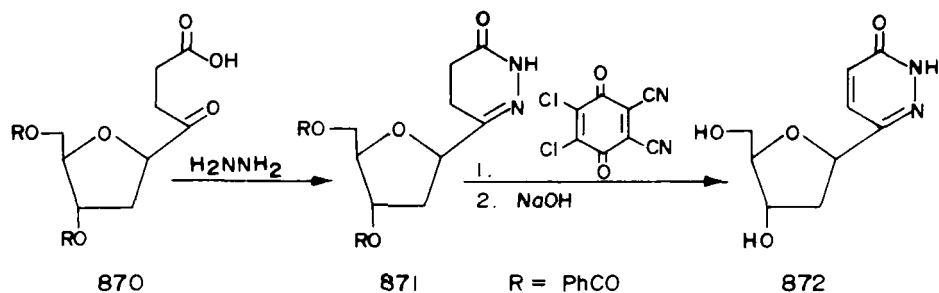
[4 + 2] Cycloaddition of the reactive 1,2,4,5-tetrazines with the glycol derivatives **884** gave the 4-(alditol-1-yl)pyridazines **886** (85LA628) (Scheme 251).



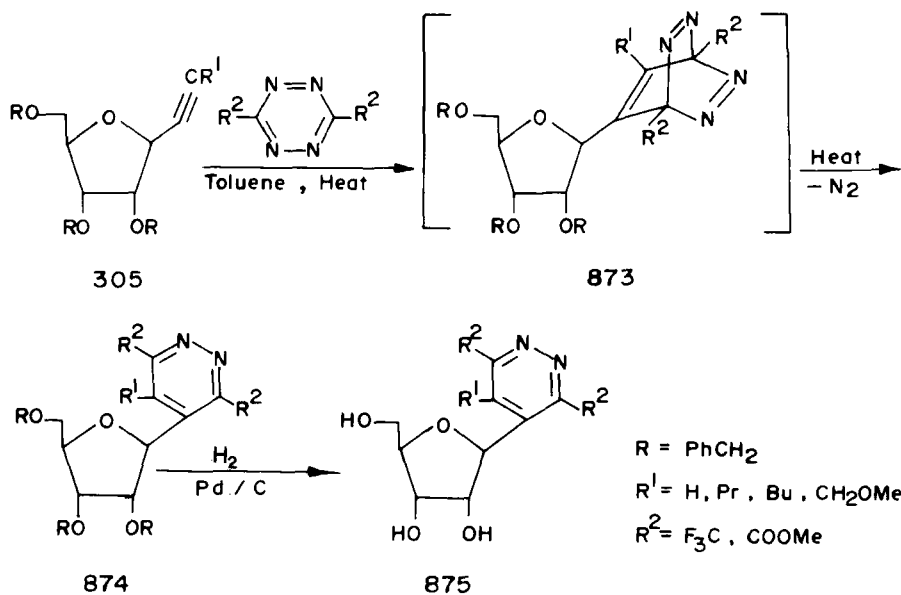
SCHEME 245



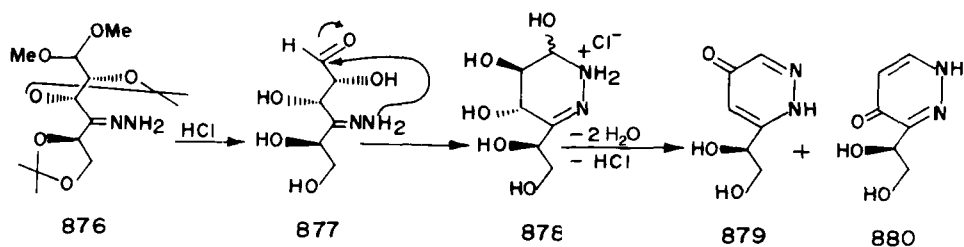
SCHEME 246



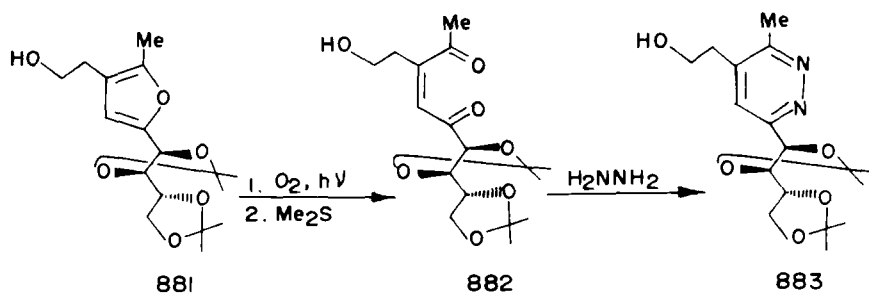
SCHEME 247



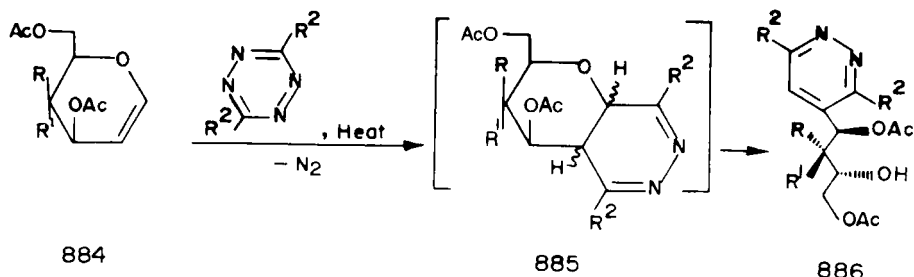
SCHEME 248



SCHEME 249



SCHEME 250



SCHEME 251

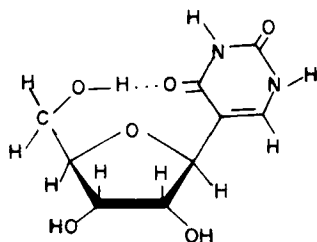
XXV. 1,3-Diazine C-Nucleosides

A. THE NATURALLY OCCURRING PYRIMIDINE C-NUCLEOSIDES "PSEUDOURIDINES" AND "EZOMYCINS"

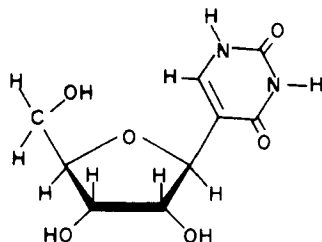
1. *Pseudouridine*

In 1951, Cohn and Volkin reported the isolation of an unknown nucleoside 5'-phosphate from enzymatically hydrolyzed calf liver transfer ribonucleic acid (51NAT483). Later, this nucleoside, named "pseudouridine" (3), as well as its 2'-, 3'-, and 5'-phosphates, was also isolated from yeast [57JBC907, 57MI1; 59BJ(72)294; 60BBA(42)244, 60JBC1488; 61MI1; 64BBA(80)361], bacteria [60BBA(42)244, 60JMB113; 64BBA-(80)361; 72B4669; 76JAN818], dog pancreas [58BBA(28)51], rat liver [59BBA(34)286], and urine of normal and diseased humans (59SCI862; 60AJM726; 63MI3, 63MI4; 67MI1). Urine of patients suffering from gout (59SCI862) and leukemia (60AJM726) and that of mentally defective patients (67MI1) was found to contain an abnormally high content of pseudouridine.

The structure of pseudouridine was established to be 5-(β -D-ribofuranosyl)uracil (3) on the basis of chemical studies [58MI1; 59BBA(32)393, 59BBA-(32)406, 59BBA(32)569; 60JBC1488; 62B490, 62MI1; 64B326; 65MI3] UV [59BBA(32)393, 59BBA(32)569], ORD [65BBR(19)643; 67B843], ^1H NMR [59BBA(32)569], ^{13}C NMR (73JHC427), and mass spectra [69BBR(35)383]. The conformations of pseudouridine in solutions have been studied by many investigators using ^1H NMR measurements (70B1557, 70JA214, 70JA4088; 72MI3; 73CJC833; 74CJC371) and molecular orbital calculations (74CJC371). Both syn (887) and anti (888) conformations were found to exist in rapid equilibrium with roughly equal populations of each. Molecular orbital calculations suggested that the syn conformation (887)



887

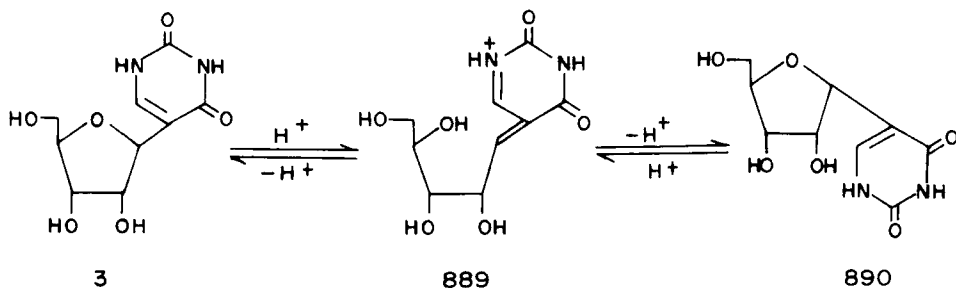


888

is stabilized by hydrogen bonding between O4 and 5'OH (74CJC371). The conformation about the exocyclic C4'—C5' bond showed preference of the gauche–gauche rotamer with 5'OH above the ribose ring.

In acid or basic media, pseudouridine (**3**) equilibrates to a mixture of its α -anomer, named α -pseudouridine (**890**) (Scheme 252) together with the α - and β -pyranoside forms (60JBC1488; 66MI1). The conformation (70JA4950; 71JA1765; 73MI1) and crystal structure (70JA4950) of α -pseudouridine (**890**) have also been studied.

The first synthesis of pseudouridine (**3**) was achieved by Shapiro and Chambers (61JA3920) by coupling tri-*O*-benzoyl-D-ribofuranosyl chloride (**63**) with 2,4-dimethoxy-5-lithiopyrimidine followed by removal of the protective groups; a mixture of the β and α anomers (**3** and **890**) was obtained as a result of isomerization induced by the acidic conditions used for deblocking (Scheme 253). Synthesis of **3** together with **890** has also been made by the acid-catalyzed cyclodehydration of a mixture of their acyclo analogs (**893**) (Section XXV,F,3) [65JCS(CC)77; 68JCS(C)1051, 68JOC140; 71JOC1507; 78LA427; 81JCS(P1)723] (Scheme 253). 2'-Deoxypseudouridine and its α -anomer have also been similarly prepared from their acyclo analogs [77JCS(CC)460].

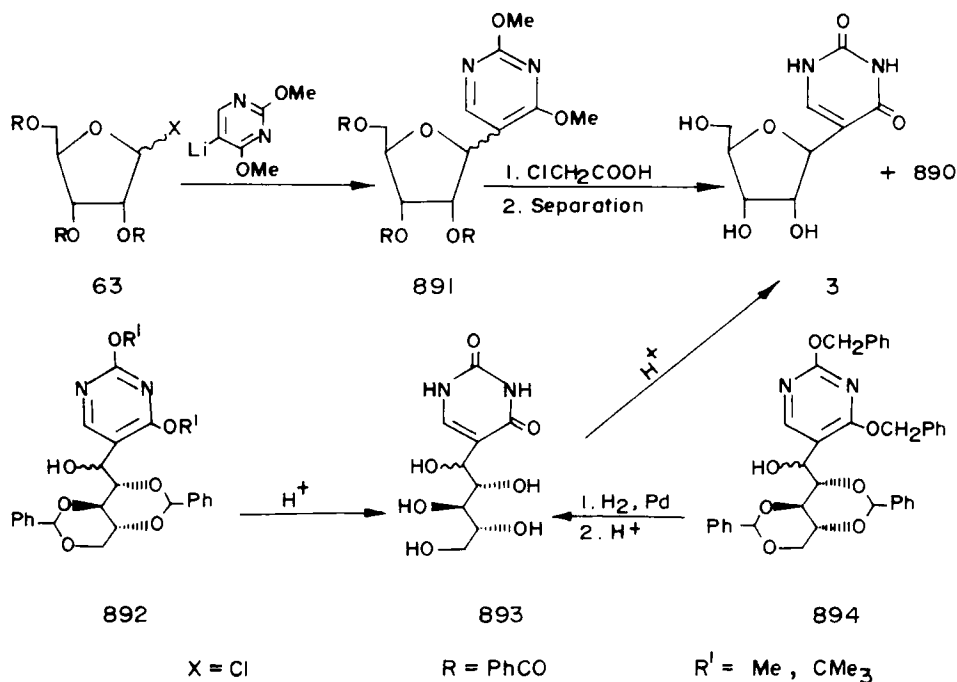


SCHEME 252

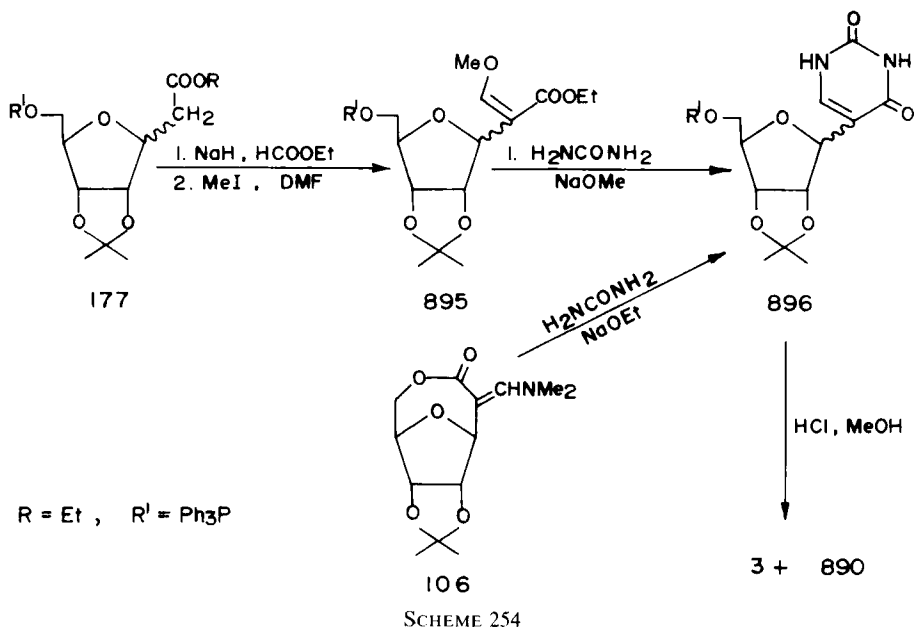
Pseudourine was prepared by constructing its uracil subunit through cyclocondensation of urea with properly functionalized C-ribofuranosyl derivatives containing three carbon side chains such as the 3-methoxy-2-(D-ribofuranosyl)acrylate **895** (76JOC2793) or the dimethylaminomethylene bicyclic lactone **106** (78JA2561; 84BCJ2515) (Scheme 254).

Pseudouridine 5'-monophosphate [61BBA(54)202], 5'-diphosphate (63-B1192), and 5'-palmitate [90JAP(K)90/196787] were prepared for exploitation in biological studies. The 5'-palmitate was applied as a hapten for the production of anti-pseudouridine monoclonal antibodies used for the immunoassay of pseudouridine in urine in early diagnosis of cancer [90JAP(K)90/196787].

The biochemistry and biosynthesis of pseudouridine and its derivatives have been the subject of many publications [60BBA(39)557, 60BBA-(44)224, 60BBA(45)163, 60BBR(3)504; 62BBA(55)798, 62BBA(61)250, 62BBA(61)799; 64MI1; 65MI4; 66BBA(119)11, 66JBC4086, 66MI2; 72BBR(46)1194; 73BBA(319)348; 74MI5].



SCHEME 253



2. 1-Methylpseudouridine

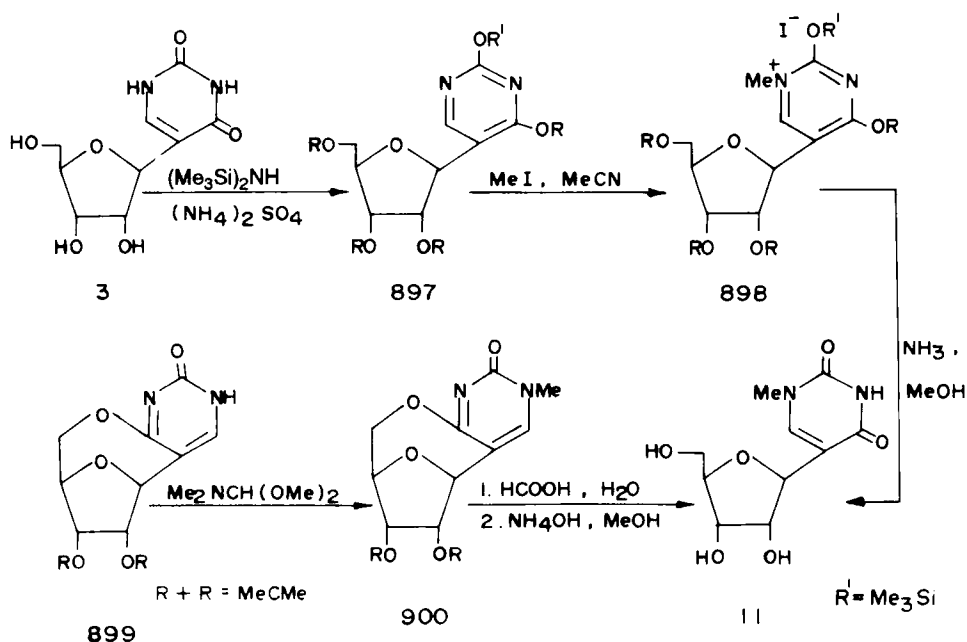
Argoudelis and Mizaak isolated this *C*-nucleoside from culture filtrates of *Streptomyces platensis* and found that its structure is 1-methyl-5-(β -D-ribofuranosyl)uracil (**11**) by studying the IR, UV, ¹H NMR, ¹³C NMR, and mass spectra of the nucleoside as well as those of its triacetate (76JAN818).

1-Methylpseudouridine (**11**) and its tri-*O*-acetyl derivative were found inactive against a variety of gram-positive and gram-negative bacteria or L-1210 leukemia cells *in vitro*, but showed marginal antiviral activity against herpes simplex (76JAN818).

1-Methylpseudouridine (**11**) was prepared by methylation of 2,4-bis(trimethylsilyl)pseudouridine (**897**) (77JAN129), the 4,5'-anhydropseudouridine derivative **899** (Section XXV,B,3) (77JAN129), or pseudouridine triacetate (77JHC699) (Scheme 255).

3. 3-Methylpseudouridine

A *C*-nucleoside isolated from the fermentation broths of *Nocardia lactamdurans* was studied and its structure established by Nielsen and Arison to be 3-methyl-5-(β -D-ribofuranosyl)uracil (**12**) (89JAN1248). Watanabe

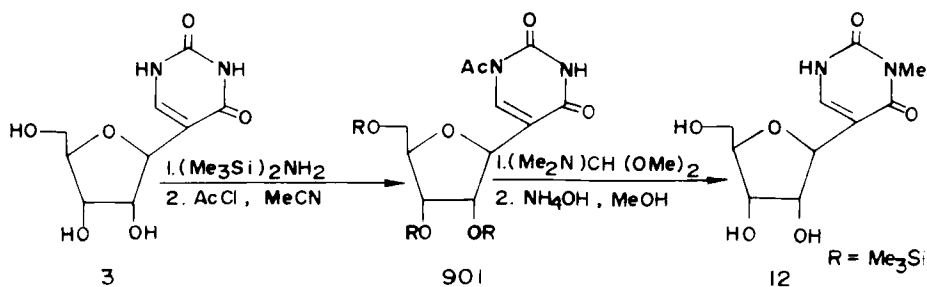


SCHEME 255

prepared **12**, prior to its isolation from the natural source, by regioselective acetylation of N1 of *O*-trimethylsilylated pseudouridine **901** followed by methylation of N3 (82MI8) (Scheme 256).

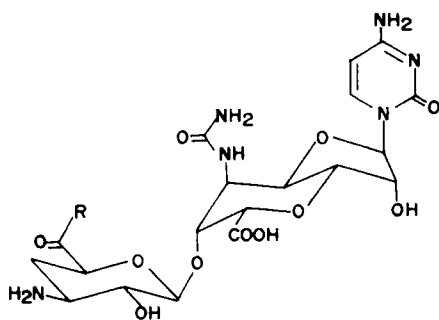
4. Ezomycins *B*₁, *B*₂, *C*₁, *C*₂, *D*₁, and *D*₂

In 1971, Takaoka, Kuwayama, and Aoki isolated a new antibiotic from culture filtrates of a strain of *Streptomyces* very similar to *S. kitazawaensis*

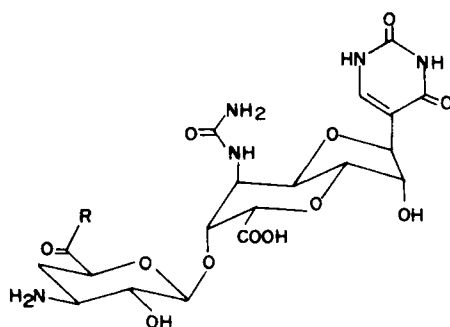


SCHEME 256

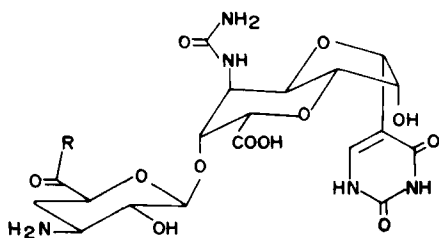
(71JAP71/615332). The antibiotic, named "ezomycin," showed antimicrobial activity against some phytopathogenic fungi such as *Sclerotinia* and *Botrytis* (71JAP71/615332). Sakata, Sakurai, and Tamura reinvestigated this antibiotic and found it to be composed of a mixture of eight components, which were designated ezomycins A₁, A₂, B₁, B₂, C₁, C₂, D₁, and D₂ (73ABC697; 74ABC1883; 75TL3191; 77ABC2027). The structures of the eight ezomycin members were established by degradative as well as by spectroscopic studies (73ABC697; 74ABC1883, 74TL1533, 74TL4327; 75ABC885, 75TL3191; 77ABC413, 77ABC2027, 77ABC2033, 77OMR230; 82MI4; 83MI3). Ezomycins A₁ (902) and A₂ (903) belong to the class of *N*-nucleosides, whereas ezomycins B₁ (904), B₂ (905), C₁ (906), C₂ (907), D₁ (908), and D₂ (909) belong to *C*-nucleosides. Ezomycins D₁ (908) and D₂ (909) were classified by some authors (81PAC129) as acyclo *C*-nucleosides; according to the definitions of *C*-nucleoside analogs (Section II), however, they should be more appropriately classified as homo *C*-nucleosides. Like pseudouridine, albeit much more easily, ezomycin B₁ readily equilibrates



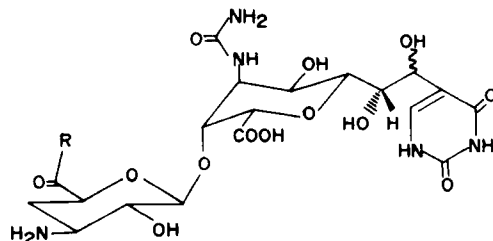
902, R = Z ; 903, R = OH



904, R = Z ; 905, R = OH

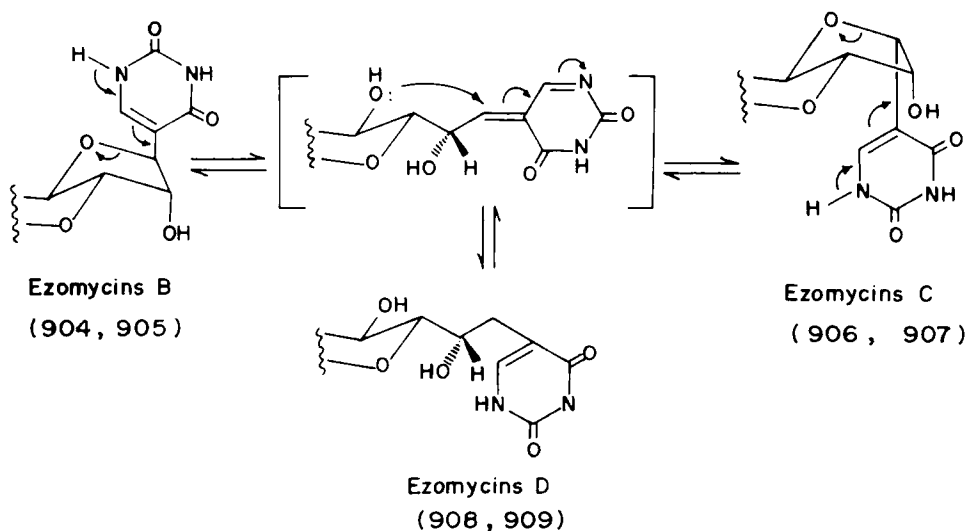


906, R = Z ; 907, R = OH



908, R = Z ; 909, R = OH





SCHEME 257

in weak acid solutions to a mixture containing ezomycins B₁, C₁, and D₁. Ezomycin B₂ also equilibrates to a mixture of B₂, C₂, and D₂ (Scheme 257). Such facile isomerization of ezomycins B takes place to mitigate the strain resulting from the trans fusion of the furanose sugar ring (75TL3191; 77ABC2033).

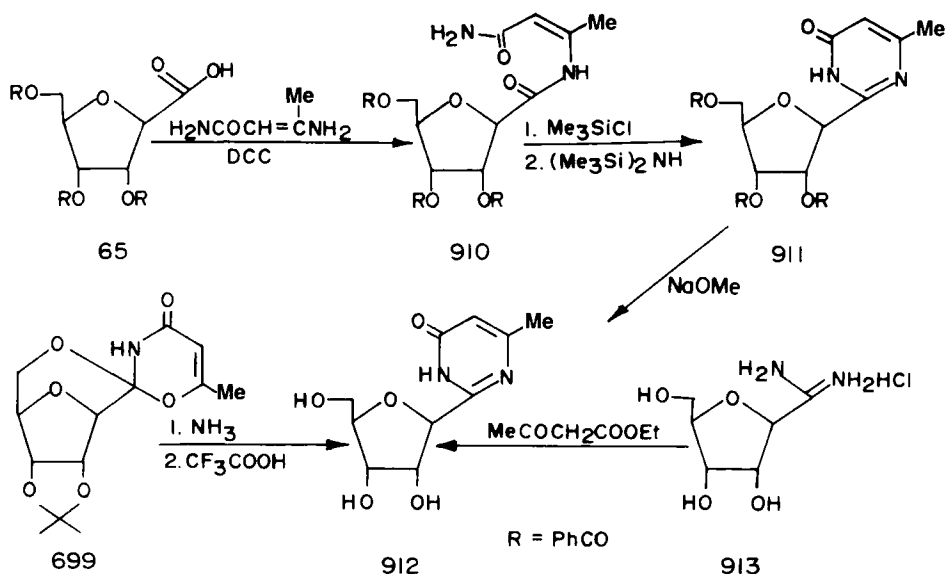
Ezomycin B₁ (904) exhibited growth inhibition activity against some strains of *Sclerotinia* and *Botrytis*; the other ezomycins are inactive (74ABC1883).

None of the ezomycins has been fully synthesized; only parts of their carbohydrate moieties were prepared [76JCS(CC)681; 77BCJ169; 81-CJC878, 81PAC129; 82MI7].

B. PYRIMIDINE C-NUCLEOSIDES

1. 2-Pyrimidinyl C-Nucleosides

Katagiri *et al.* prepared the 2-pyrimidyl C-nucleoside **912** by two routes (85CPB102); the first involved reaction of the 2,5-anhydro-D-allonic acid derivative **65** with 3-aminocrotonamide followed by cyclization and removal of the protective groups. The second route comprised oxazine ring opening of the spiro compound **699** with ammonia. Riley obtained the same C-



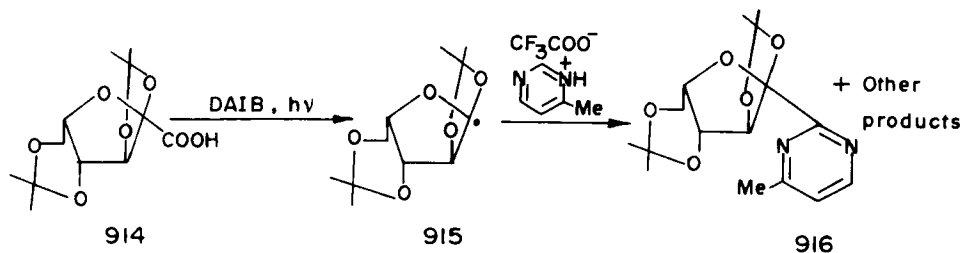
SCHEME 258

nucleoside (**912**) by cyclization of 2,5-anhydroallonamidine (**913**) with ethyl acetoacetate (87JHC955) (Scheme 258).

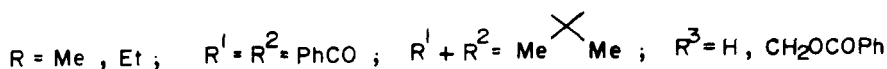
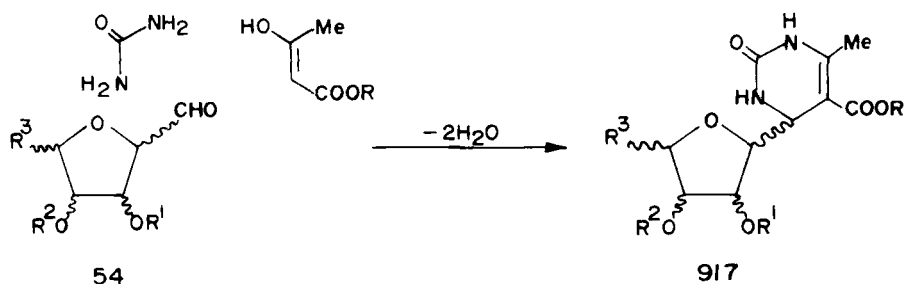
Coupling the saccharide free radical **915** with 4-methylpyrimidine trifluoroacetate gave a mixture of the 2-pyrimidinyl **916** and 4(6)-pyrimidinyl C-nucleosides in which the later preponderated (92TL7575) (Scheme 259).

2. 4(6)-Pyrimidinyl C-Nucleosides

A number of tetrahydropyridin-4-yl C-nucleosides (**917**) were prepared by Spanish workers by an adaptation of the Biginelli reaction according to



SCHEME 259



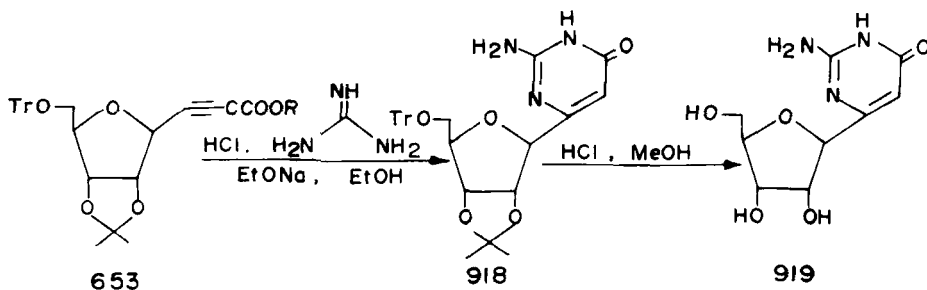
SCHEME 260

which mixtures of 2,5-anhydropentose or 2,5-anhydrohexose derivatives (**54**), acetoacetic esters, and urea reacted together [78AQ553; 81AQ(C)147, 81AQ(C)348; 82AQ(C)250; 84AQ(C)218] (Scheme 260).

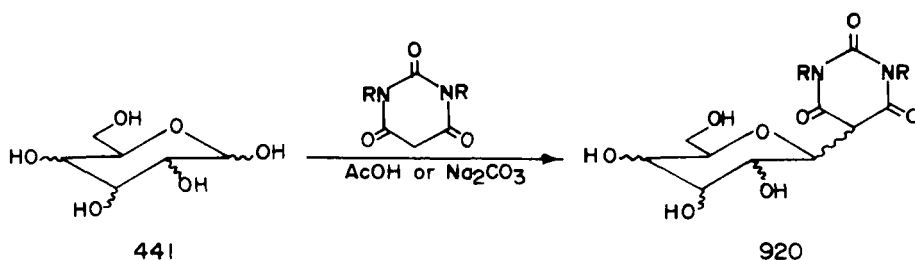
The pyrimidin-4-yl subunit of nucleoside **918** was assembled on the 3-(β -D-ribofuranosyl)propiolate ester **653** by cyclocondensation with guanidine hydrochloride (75TL3271, 79JOC4854) (Scheme 261).

3. 5-Pyrimidinyl C-Nucleosides

Pyrimidin-5-yl C-nucleosides are the most widely studied class of pyrimidine C-nucleosides; all of the general approaches of C-nucleoside synthesis were applied in their preparation. Thus, reaction of unprotected aldohexopyranoses (**441**) with pyrimidin-4-ones (80MI2) or barbituric acid derivatives (86MI4; 94MI5) gave 5-(α - or β -glycopyranosyl)uracils (**920**) or their acyclo analogs (Section XXV,F,3) depending on the nature of the two reacting entities (Scheme 262).



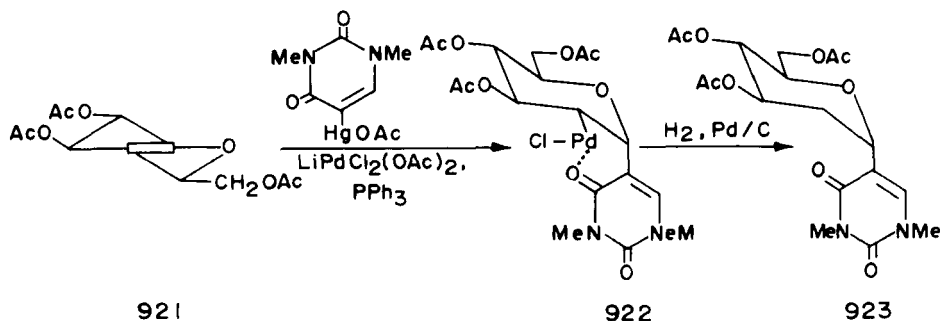
SCHEME 261



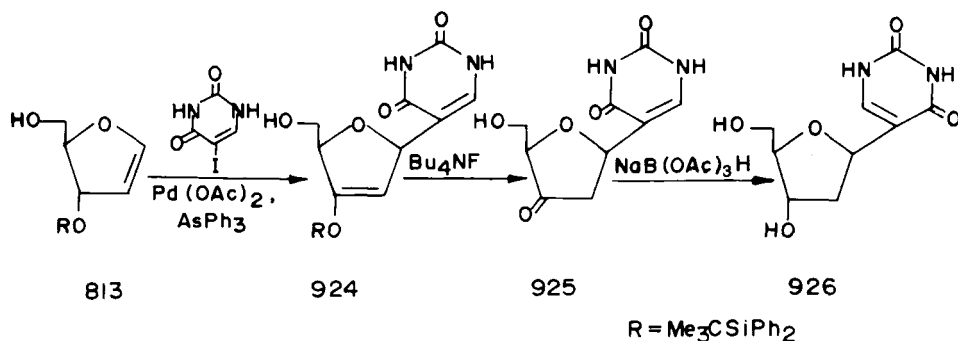
SCHEME 262

Daves and his group thoroughly studied the regio- and stereospecific outcome of the palladium-mediated coupling of furanoid and pyranoid glycal (1,2-unsaturated sugars) derivatives (e.g., **921**) with 5-pyrimidinyl-mercuric acetates followed by hydrogenolysis of the resultant organopalladium adducts **922** to produce 2'-deoxypyrimidin-5-yl *C*-nucleosides (**923**) (78JA287; 81JA7683; 83JOC2870; 85JA6476; 86JOC3093, 86MI5; 87JOC3083; 90MI8) (Scheme 263). This reaction was regiospecific because carbon-carbon bond formation takes place solely between C5 of the pyrimidine ring and the electron-deficient C1 of the glycal. It is also stereospecific because the heteropalladium salt adds in a syn fashion onto the least sterically hindered face of the glycal ring. Consequently, the relative steric bulk of the substituents at C3 and C5 of furanoid glycals or at C3, C4, and C6 of pyranoids glycals controls the α or β configuration of the resulting *C*-nucleoside as a result of affecting access to the two respective faces of the glycal.

Palladium-mediated coupling of 5-idouracil with the furanoid glycal derivative **813**, so designed to ensure stereospecific β -*C*-glycosyl bond formation, gave **924**. Desilylation of **924** afforded 2'-deoxy-3'-ketopseudouridine



SCHEME 263



SCHEME 264

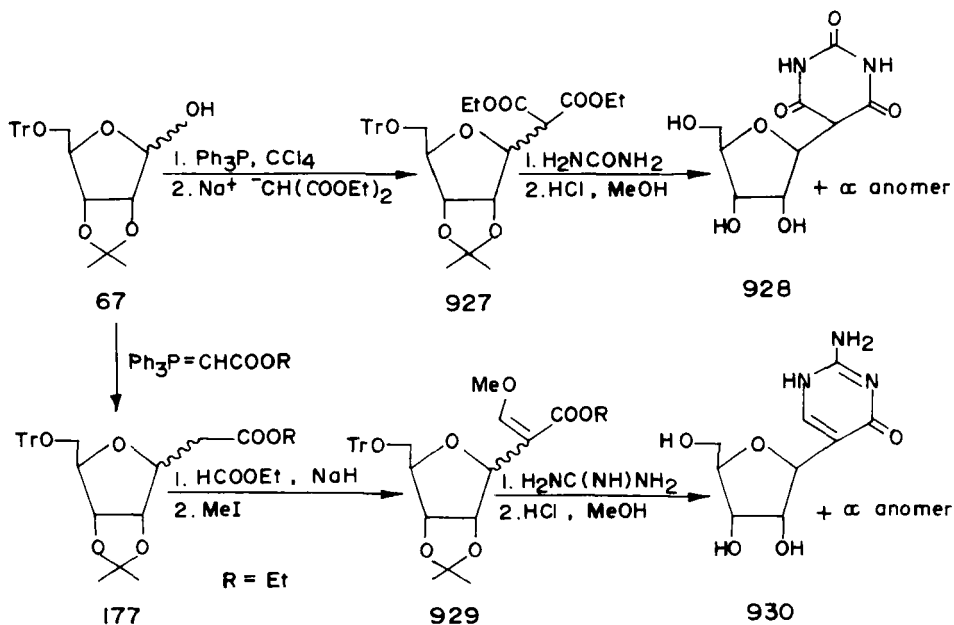
925, which was stereospecifically reduced to 2'-deoxypseudouridine **926** (92JOC4690; 93JOC2557) (Scheme 264).

Frequently used for the synthesis of pyrimidin-5-yl C-nucleosides was the cyclocondensation of urea derivatives with C-glycosyl derivatives having a three-carbon appendage such as the 2-(D-ribofuranosyl)malonic ester **927** (73TL1951) and the 3-methoxy-2-(D-ribofuranosyl)acrylate ester **929** (75JHC817; 77GEP26017555; 93MI4) or its D-arabinofuranosyl congener (78JMC96), as well as 3-methoxyl(D-ribofuranosyl)acrylonitrile (77JOC711); nucleosides **928** and pseudoisocytidine (**930**) were obtained, respectively (Scheme 265).

Pseudoisocytidine (**930**) exhibited excellent antitumor activities (76MI7; 79MI3, 79MI7), yet clinical trials revealed that it causes severe hepatotoxicity (80MI5). Interestingly, the D-arabino analog of **930** was inactive (78JMC96).

In a series of publications Noyori *et al.* reported the synthesis of 2-thiopseudouridine (**931**), pseudoisocytidine (**933**) (78JA2561; 84BCJ2515), and their branched sugar analogs, namely, 1'-alkyl- (79TL2897), 2'-alkyl- (80TL1971; 81H321), 4'-alkyl- (78MI4; 79TL2897; 80H761, 80TL2535), 1',4'-dialkyl- (80CL679; 83BCJ2680), 5'-alkyl-, and 5,5'-dialkyl- (78CL1297, 78TL4403; 83BCJ2680) 2-thiopseudouridines (**931**) and pseudoisocytidines (**933**) by the reaction of the corresponding rigid bicyclic lactone **932** with thiourea or guanidine. This reaction stereospecifically produced the β C-nucleosides as a result of the rigidity of the bicyclic lactones **932** (Scheme 266).

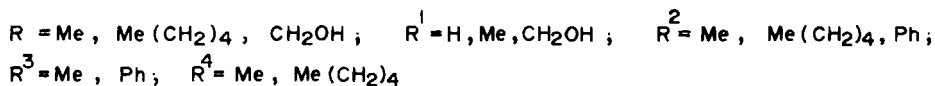
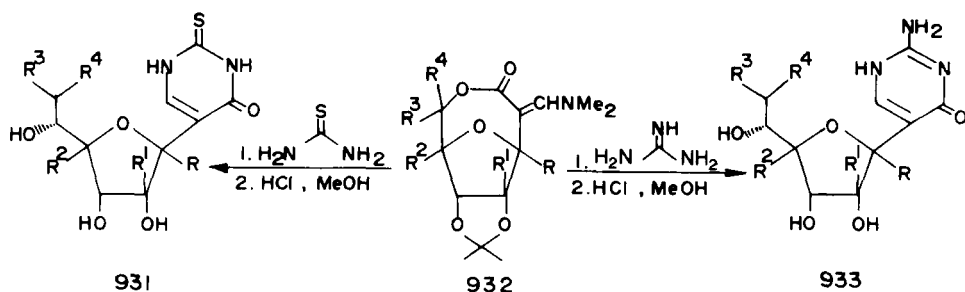
Removal of the protective groups of the pyrimidin-5-yl acyclo C-nucleoside **934** (Section XXV.F,3) followed by acid-catalyzed cyclodehydration of the resulting polyhydroxyl chain of **935** gave **936** (66JOC2215) (Scheme 267). 5-(β -xylofuranosyl)uracil (66JOC2215), 5-(β -D-ribofuranosyl)cytosine (pseudocytidine) [72CR(C)331], and 2'-deoxypseudouridine [77JC-



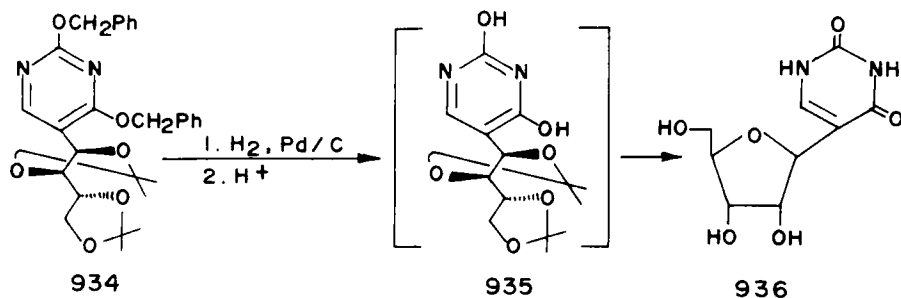
SCHEME 265

S(CC)460; 78MI3] were similarly prepared from the corresponding acyclo analogs.

Base-catalyzed displacement of the sulfonyloxy groups of a mixture of the protected 5-(2-deoxy-D-*allo*- and 2-deoxy-D-*altro*-pentitol-1-yl)uracils **937** took place by an intramolecular $\text{S}_{\text{N}}2$ mechanism and afforded the two pyranoside C-nucleosides **938** and **939** (78MI3) (Scheme 268).



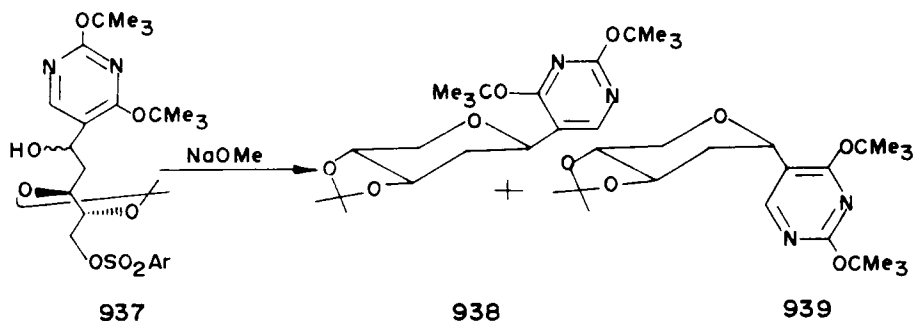
SCHEME 266



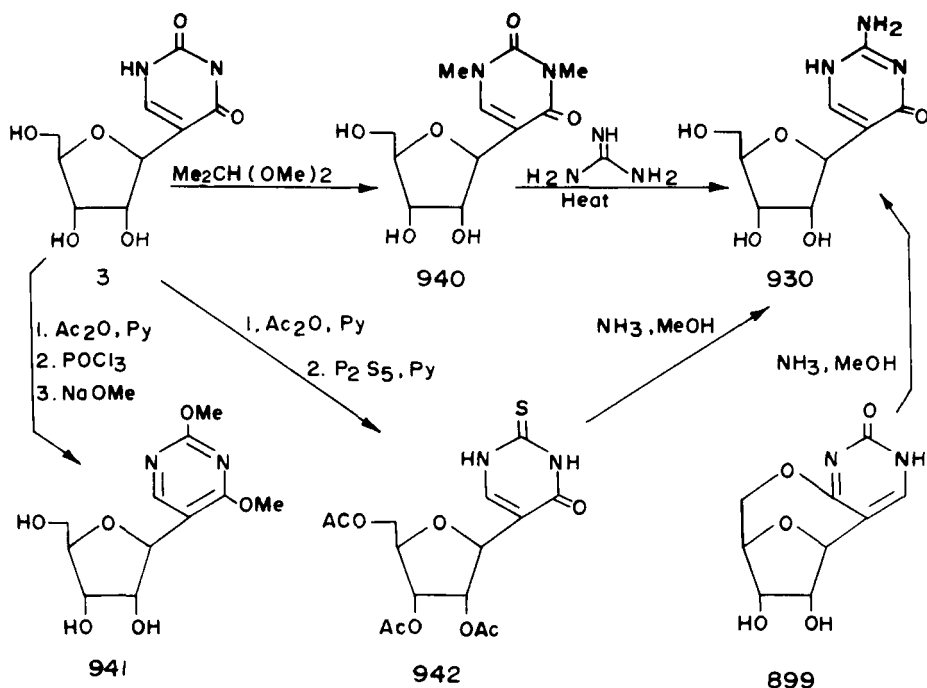
SCHEME 267

Substantial research work was aimed at the synthesis of pyrimidin-5-yl C-nucleosides using the approach of nucleoside–nucleoside transformation and involved alteration in the pyrimidine or sugar subunits, or both, of readily accessible members. Among the modifications involving the pyrimidine moiety was the preparation of pseudoisocytidine (**930**) from 1,3-dimethylpseudouridine (**940**) (77JHC537; 78JOC1193), 2-thiopseudouridine acetate (**942**) [78JAP(K)78/108982], or 4,5'-anhydropseudouridine (**899**) (84MI4). Pseudouridine (**3**) has also been transformed to the antileukemic 2,4-dimethoxypyrimidin-5-yl C-nucleoside **941** (78USP4092472) (Scheme 269).

Of the alterations that involved the sugar and the pyrimidine moieties, one is the anhydro ring formation between the two subunits. Pseudouridine (**3**) forms three types of anhydro compounds, namely, 4,2'-, 4,3'-, and 4,5'-anhydro derivatives. Treatment of **3** with salicyl chloride or α -acetoxyisobutyryl chloride gave a mixture of the 4,2'-anhydro derivative **943** together with the 2'-chloro-2'-deoxypseudouridine **944**. This mixture



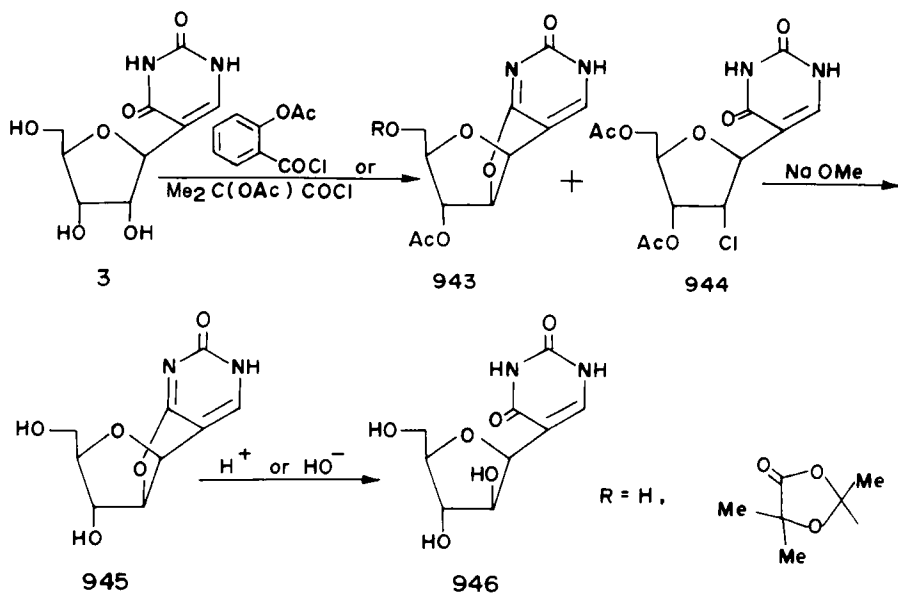
SCHEME 268



SCHEME 269

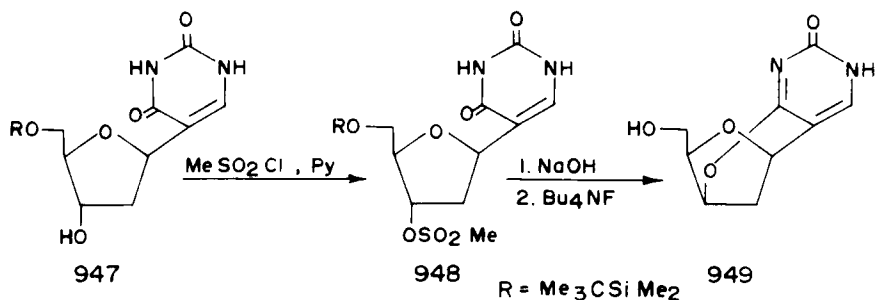
afforded the 4,2'-anhydropseudouridine **945** upon treatment with sodium methoxide under mild conditions (76JHC933; 77JHC1119; 78JMC96; 85MI12). Acid- or base-induced anhydro ring opening of **945** gave the *D*-*arabino* analog **946** known as *ara*-pseudouridine (76JHC933; 78JMC96) (Scheme 270). 4,2'-Anhydropseudoisocytidine (76JHC933) and *ara*-pseudoisocytidine (76JHC933; 78JMC96) were obtained by similar reactions. 4,3'-Anhydro-2'deoxypseudouridine **949** was prepared from the 3'-methylsulfonyloxy derivative **948** by treatment with sodium hydroxide (88JOC2777) (Scheme 271). 4,5'-Anhydropseudouridine **899** was obtained from 5'-(4-tolylsulfonyloxy)pseudouridine **950** by the sequence of reactions shown in Scheme 272 (84MI4) and 4,5'-anhydro-1-methylpseudouridine was similarly prepared (85JOC3319).

2'-Deoxypseudouridine (**954**) was prepared by reductive removal of the 2'-*O*-thiocarbonylimidazolyl group of derivative **953** with tributyltin hydride (82JOC485; 91MI18), and its conformation was studied (94JOC-6629) (Scheme 273). Also prepared according to this scheme were 1-methyl- (82JOC485; 91MI18), 3-methyl- (82MI8), and 1,3-dimethyl-2'-

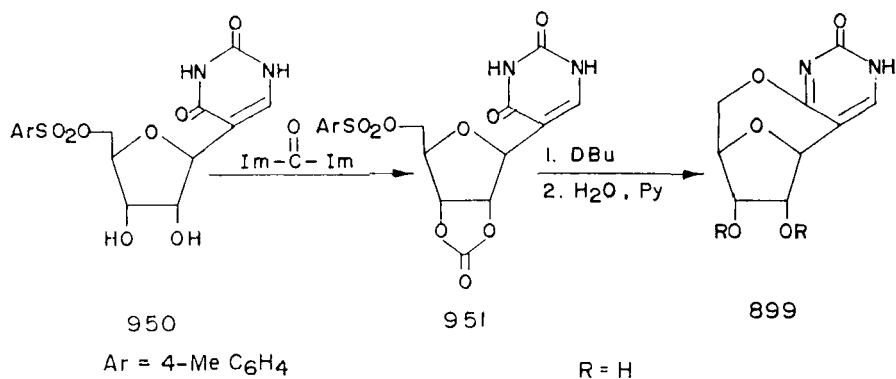


SCHEME 270

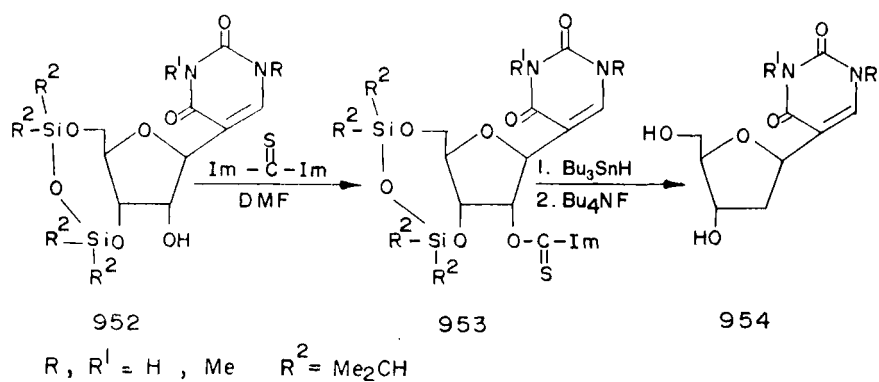
deoxypseudouridines (82JOC485; 88JOC2777) and 2'-deoxypseudoisocytidine (82JOC485). Reductive dechlorination of a mixture of 2'-chloro- (**955**) and 3'-chloro-3-deoxypseudouridines (**956**) with tributyltin hydride gave a separable mixture of 2'-deoxy- (**954**) and 3'-deoxypseudouridines (**957**) [78JCS(CC)677; 81JOC3603] (Scheme 274). This reaction was also applied to pure **955** to furnish **954** [77JCS(CC)460, 77JHC1119; 78MI3]. 2'-Deoxypseudouridine-5'-phosphate was enzymatically prepared [72BB(46)1194; 77BBA(281)1119] and found to inhibit thymidylate synthetase [72BBR(46)1194]. 2'-Deoxy-1-methylpseudouridine inhibited the growth of *Streptococcus faecium* and P815 tumor cells (77JHC1119).



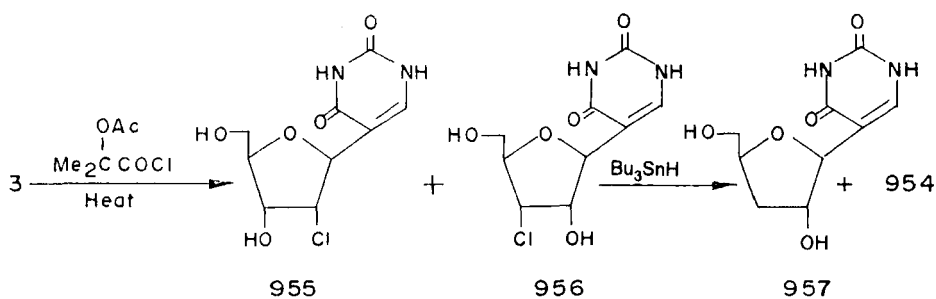
SCHEME 271



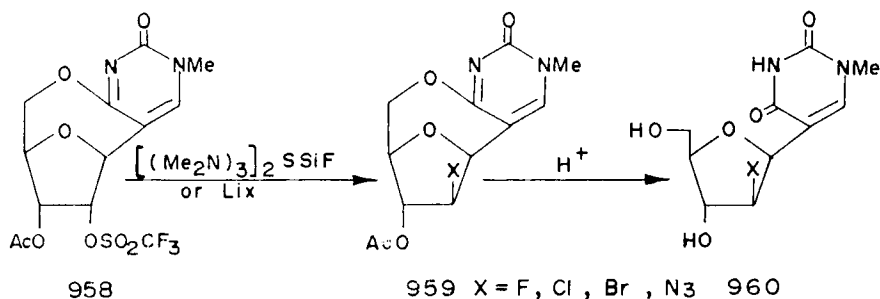
SCHEME 272



SCHEME 273



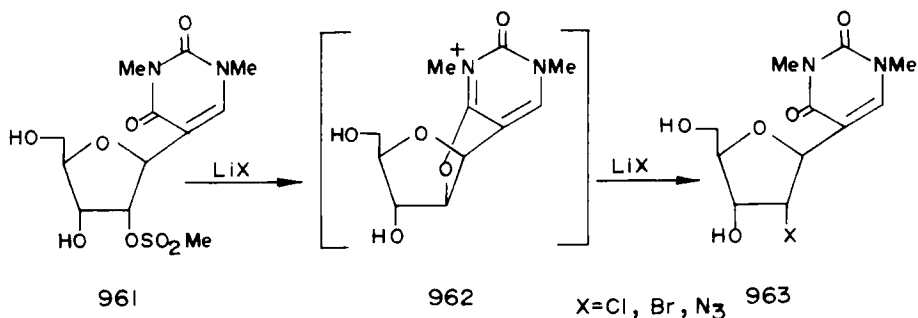
SCHEME 274



SCHEME 275

Nucleophilic displacement of *O*-sulfonyl derivatives of pyrimidin-5-yl *C*-nucleosides was employed to prepare their halo and azido derivatives. Thus, the 2'-sulfonyloxy derivative **958** gave 2'-halo-2'-deoxy (**960**, R = F, Cl, Br) and 2'-azido-2'-deoxy (**960**, R = N₃) *C*-nucleosides with inverted configuration at C2' (85JOC3319; 87JMC2314) (Scheme 275). In contrast, the 2'-sulfonyloxy derivative **961** underwent such displacements without configurational inversion to give **963**; double inversion through the 4,2'-anhydro intermediate **962** was suggested to explain these results (82MI5; 85JHC1703) (Scheme 276).

Similar displacements were performed on 3'-sulfonyloxy- (88JOC2777; 90JMC1995) and 5'-sulfonyloxypyrimidin-5-yl C-nucleosides (80MI10; 82MI6; 85JHC1703; 88JOC5046). 2'-Deoxy-2'-fluoropseudouridine showed antiviral activity *in vitro* but failed *in vivo* (87JMC2314); all of the 5'-deoxy-5'-halopseudouridines were inactive against L-1210 leukemia cells; and 3'-azido-2', 3'-dideoxy-l-methylpseudourine (C-AZT) was inactive against HIV (90JMC1995).



SCHEME 276

C. PYRIMIDINE HOMO C-NUCLEOSIDES

1. 4(6)-Pyrimidinyl Homo C-Nucleosides

The 4-(D-ribofuranosyl)-3-oxobutanoate derivative **964** cyclocondensed with urea or its derivatives to produce the pyrimidin-4-yl homo C-nucleosides **965** (78JOC2925; 82JOC5115) (Scheme 277).

Synthesis from preformed pyrimidines was made by condensation of *aldehydo-sugar* derivatives (**67**) with (pyrimidin-4-yl)methylene phosphoranes to afford anomeric mixtures of pyrimidin-4-yl homo C-nucleosides (**968**) [83JCS(P1)201; 86JOC1058, 86LA957; 89JCS(P1)2401] (Scheme 278). Very similar to this reaction is the condensation of glycosyl halides with 4-lithiomethylene pyrimidines (94GEPDE4320570).

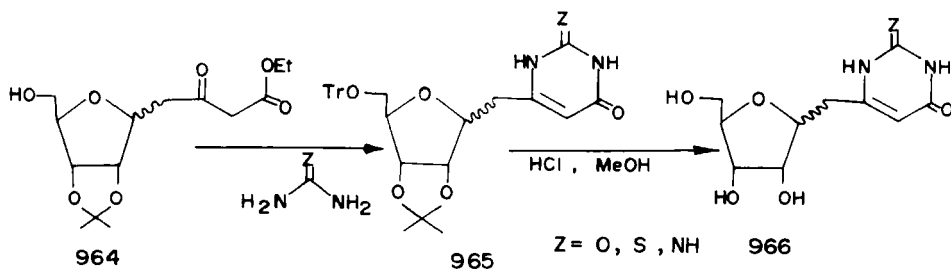
2. 5-Pyrimidinyl Homo C-Nucleosides

The pyrimidine rings of **970** were built on the 2-formyl-3-(β-D-ribofuranosyl)propanoate enol ether derivative **969** by reaction with urea, thiourea, or guanidine (79MI2, 79TL3669; 83BCJ2700) (Scheme 279).

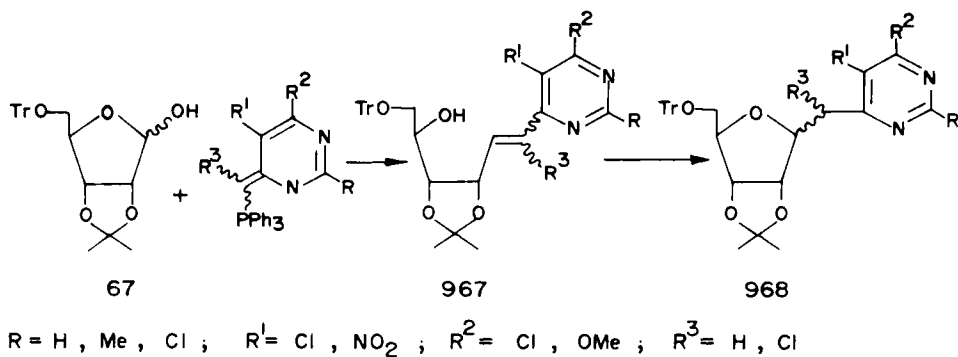
D. PYRIMIDINE CARBOCYCLIC C-NUCLEOSIDES

1. 4(6)-Pyrimidinyl Carbocyclic C-Nucleosides

Similar to the preparation of the 2-pyridyl carbocyclic C-nucleoside **829** (Section XXIII.C; Scheme 231), coupling the 2,3-benzyloxycyclobutane free radical **828** with pyrimidinium trifluoroacetate gave the corresponding 4-pyrimidinyl 2,3-dibenzyloxycyclobutyl C-nucleoside [94JCS(P1)2407].



SCHEME 277



SCHEME 278

2. 5-Pyrimidinyl Carbocyclic C-Nucleosides

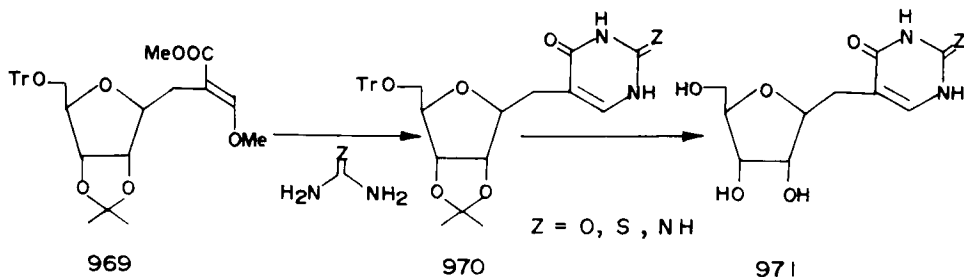
The carbobicyclic lactone derivative **972** underwent 2-thiouracil ring formation when reacted with thiourea to give the carbocyclic 2-thiopseudouridine **973**, which was desulfurized to **974** (75JOC2488) (Scheme 280).

A molecule of benzamidine supplemented the remaining part of the pyrimidine ring to the carbocyclic malonic ester derivative **975** to give **976** (86CPB4875, 86MI1) (Scheme 281).

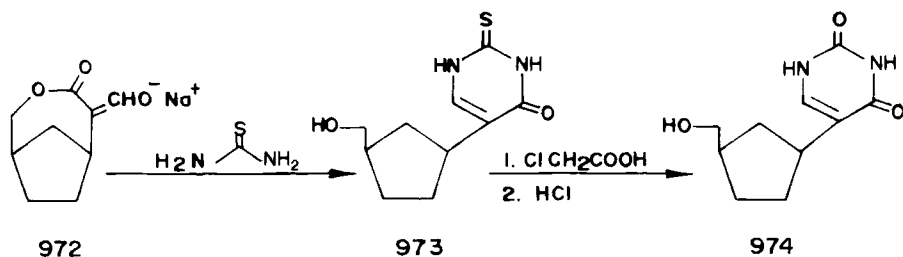
E. PYRIMIDINE REVERSE C-NUCLEOSIDES

1. 4(6)-Pyrimidinyl Reverse C-Nucleosides

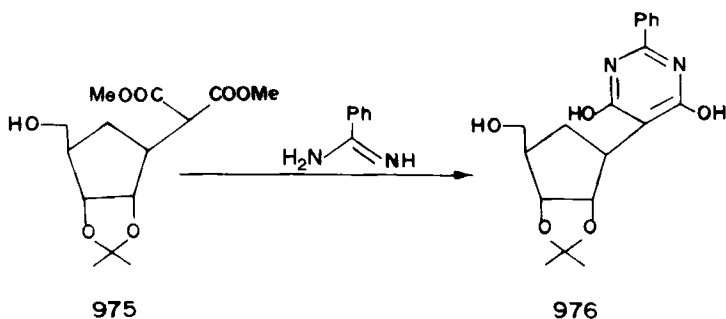
Reaction of the aldehyde group of **977** with the methyl function of 2,4-dimethoxy-6-methylpyrimidine gave the 4-pyrimidinyl reverse C-nucleoside **978**, which was deoxygenated to **979** (89CPB660) (Scheme 282).



SCHEME 279



SCHEME 280

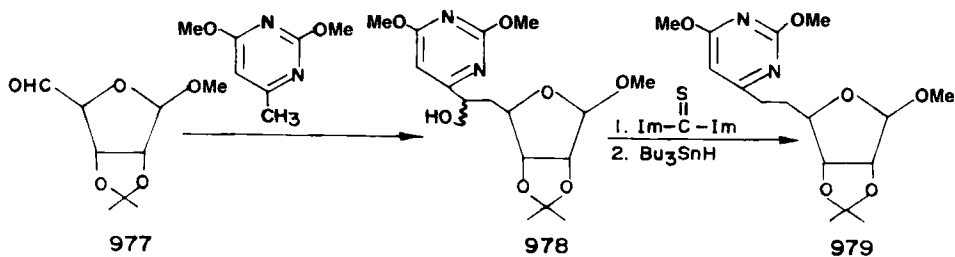


SCHEME 281

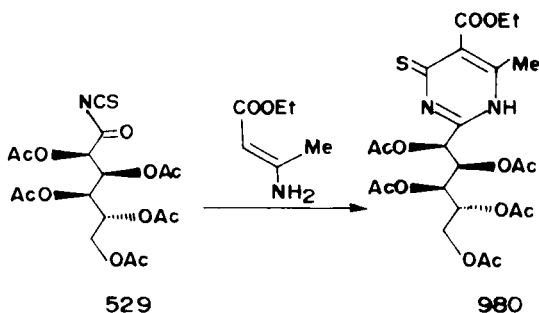
F. PYRIMIDINE ACYCLO C-NUCLEOSIDES

1. 2-Pyrimidinyl Acyclo C-Nucleosides

D-Gluconoyl isothiocyanate pentaacetate (**529**) cyclocondensed with ethyl 3-aminocrotonate to give **980** (81CPB1832) (Scheme 283).



SCHEME 282



SCHEME 283

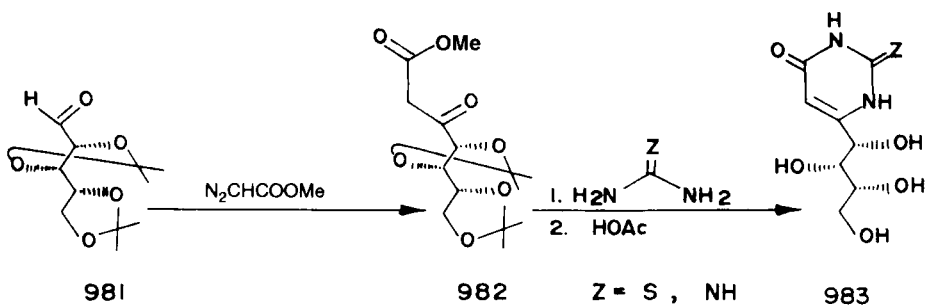
2. 4(6)-Pyrimidinyl Acyclo C-Nucleosides

Aldonoyl acetic esters (**982**), obtained from *aldehydo*-sugar derivatives such as **981** and diazoacetic ester, condensed with urea derivatives to give the corresponding 4-(alditol-1-yl)pyrimidines **983** [79MI9; 84AQ(C)45] (Scheme 284).

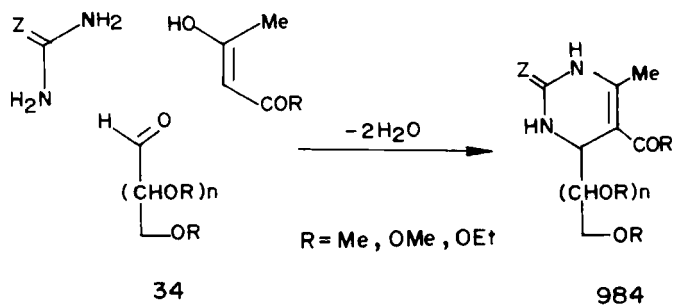
Biginelli reaction was applied for the preparation of 4-(alditol-1-yl)tetrahydropyrimidines (**984**) by reacting a ternary mixture of *aldehydo*-sugar derivatives (**34**), urea or thiourea, and 1,3-dicarbonyl compounds [79MI10; 81AQ(C)147; 86H679] (Scheme 285).

3. 5-Pyrimidinyl Acyclo C-Nucleosides

Condensation of 5-lithiopyrimidines with *aldehydo*-sugar derivatives (**226**) is the method of choice for the synthesis of this category of C-nucleosides [65JCS(CC)77; 66JOC2215; 68JCS(C)1051; 71JOC1507;



SCHEME 284

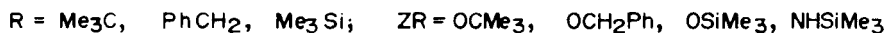
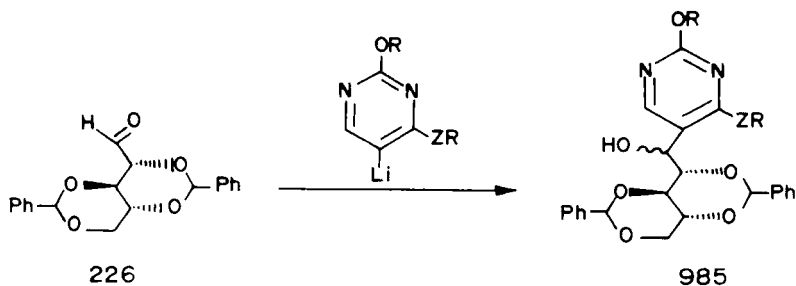


SCHEME 285

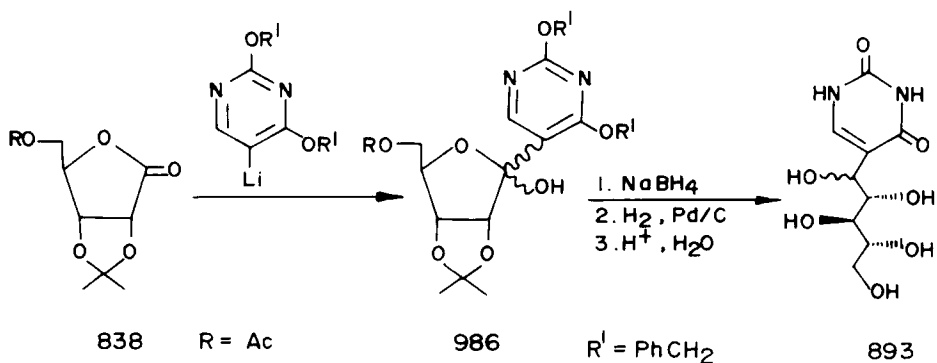
72CR(C)331; 73MI5; 77JCS(CC)460; 78LA427, 78MI3; 81JCS(P1)723]; a mixture of the two possible stereoisomeric products **985** was obtained (Scheme 286).

The aldolactone derivative **838** also reacted with 5-lithiopyrimidines to give a mixture of the two hemiacetal C-nucleosides **986**. Reduction of the latter with sodium borohydride and removal of the protective groups gave the corresponding acyclo analogs **893** (68JOC140) (Scheme 287).

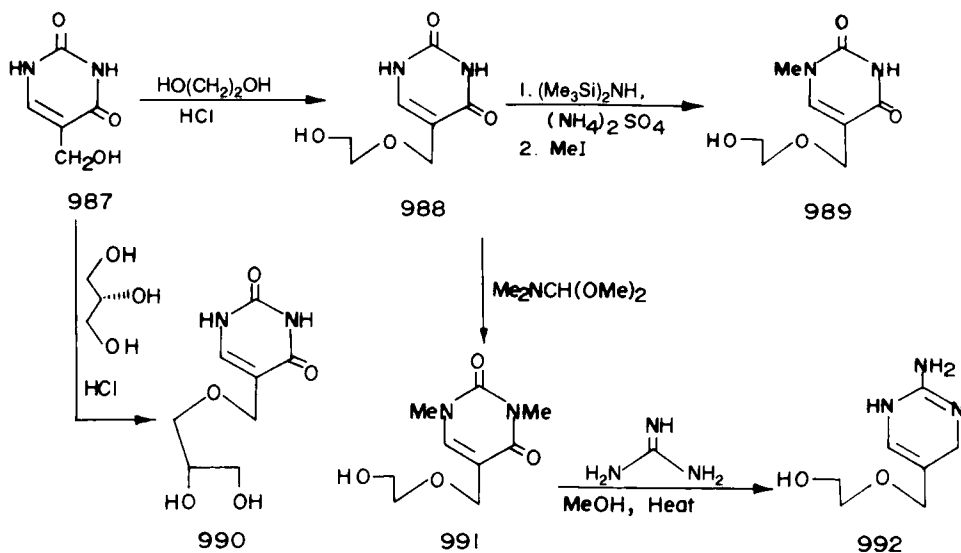
Acyclopseudouridines with truncated sugar residues such as **988** (83MI1; 84JHC9) and **990** (86JHC1621; 91MI19) were prepared by chain elongation at the hydroxymethyl group of **987**. Compound **988** was transformed to acyclo 1-methyl- (**989**), 1,3-dimethylpseudouridines (**991**), and acyclo pseudoisocytidine (**992**) (84JHC9; 86JHC1621) (Scheme 288). None of these compounds showed any significant activity against herpes viruses or L-1210 mouse leukemic cells (83MI1; 84JHC9; 86JHC1621).



SCHEME 286



SCHEME 287

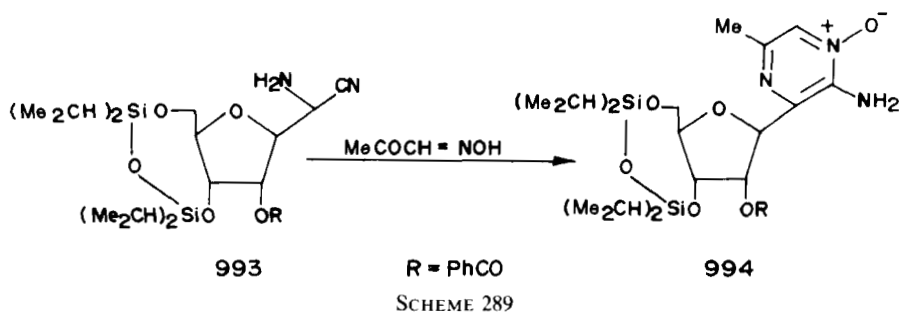


SCHEME 288

XXVI. 1,4-Diazine C-Nucleosides

A. PYRAZINE C-NUCLEOSIDES

A single example of this type (**994**) was recently synthesized by cyclocondensation of the 2-amino-2-(β -D-ribofuranosyl)acetonitrile derivative **993** with 2-methylglyoxal-1-oxime (94JA6929) (Scheme 289).

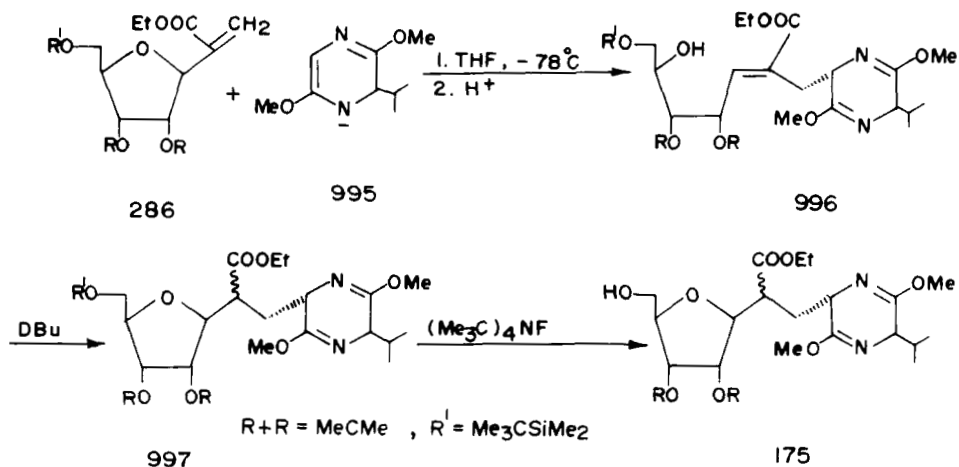


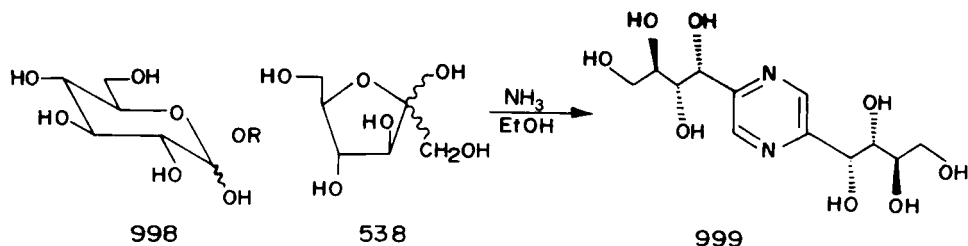
B. PYRAZINE HOMO C-NUCLEOSIDES

The pyrazine bis-homo C-nucleoside **175** was prepared by addition of the 2-(β -D-ribofuranosyl)acrylate derivative **286** to the pyrazine anion **995** (88TL375) (Scheme 290).

C. PYRAZINE ACYCLO C-NUCLEOSIDES

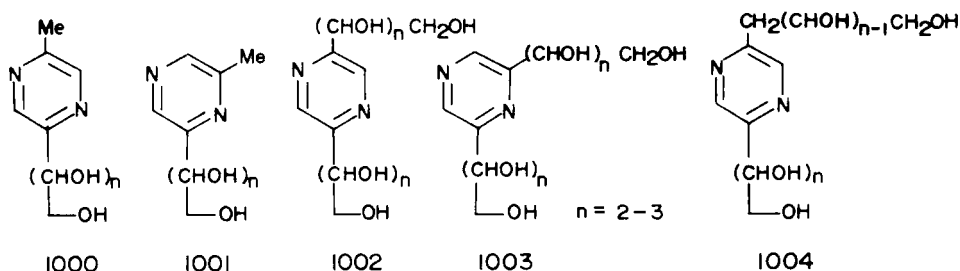
These compounds have long been known since Lobry de Bruyn (1899RTC72) investigated the browning reaction of D-glucose (**998**) and D-fructose (**538**) in the presence of alcoholic ammonia. From the complex reaction mixtures 2,5-di-(D-arabino-tetritol-1-yl)pyrazine (**999**) was isolated





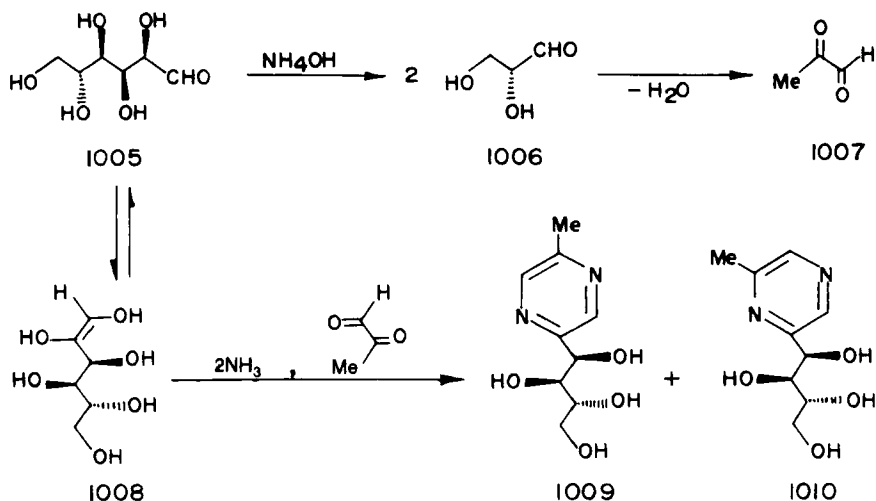
SCHEME 291

and named "fructosazine" (Scheme 291). This reaction has been reinvestigated by many research groups using the neutral sugars; D-glucose (08MI1; 52JCS3854; 73ABC2571; 75ABC1143), D-fructose (08MI1; 35CB2187; 76ABC921), L-sorbose (73MI3), D-xylose (76ABC1241), and sucrose (67MI2). The reaction has also been studied with the penta-*O*-nicotinoyl derivatives of D-glucose (72MI9) and D-mannose (72MI4), as well as tetra-*O*-nicotinoyl-D-xylose (73MI8). In addition to alcoholic ammonia (08MI1; 35CB2187), aqueous ammonia (52JCS3854; 73MI3), aqueous ammonium formate (76ABC1241), and aqueous urea (67MI2) have been used. One or more of the five types of alditolpyrazines **1000–1004** were isolated



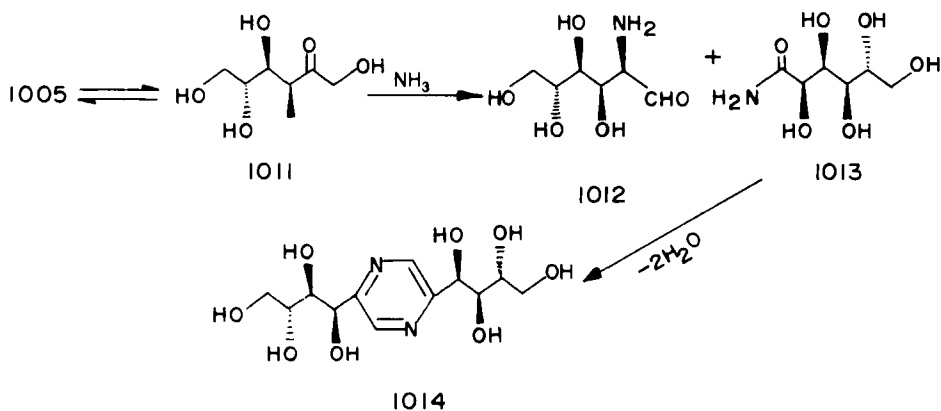
from the reaction mixture. Structures of the obtained alditolpyrazines were determined by oxidation to known pyrazine dicarboxylic acids, and mechanisms were proposed for their formation. Thus, the formation of 2-methyl-5- and 6-(D-arabino-tetritol-yl)pyrazines (**1009** and **1010**) from aldehydo-D-glucose (**1005**) involved the condensation of **1005** and methylglyoxal (**1007**) with ammonia; methylglyoxal resulted from the fission of the hexose molecule (**1005**) to two molecules of glyceraldehyde (**1006**) (52JCS3854) (Scheme 292).

The mechanism proposed for the formation of 2,5-di-(D-arabino-tetritol-1-yl)pyrazine (**1014**) from D-glucose (**1005**) (Scheme 293) assumed the for-



SCHEME 292

mation of 2-amino-2-deoxy-D-glucose (**1012**) and 1-amino-1-deoxy-D-fructose (**1013**), which condensed together to give **1014** (72MI9). The reaction of ammonia with the basic sugars 1-amino-1-deoxy-D-glucose (35CB2187), 2-amino-2-deoxy-D-glucose [61JCS2468, 61LA(644)122; 66JOC2239; 79MI16, 79MI17; 82JOC4772; 91CPB792], 2-amino-2-deoxy-D-mannose (66JOC2239; 93T2655), and 2-amino-2-deoxy-D-galactose



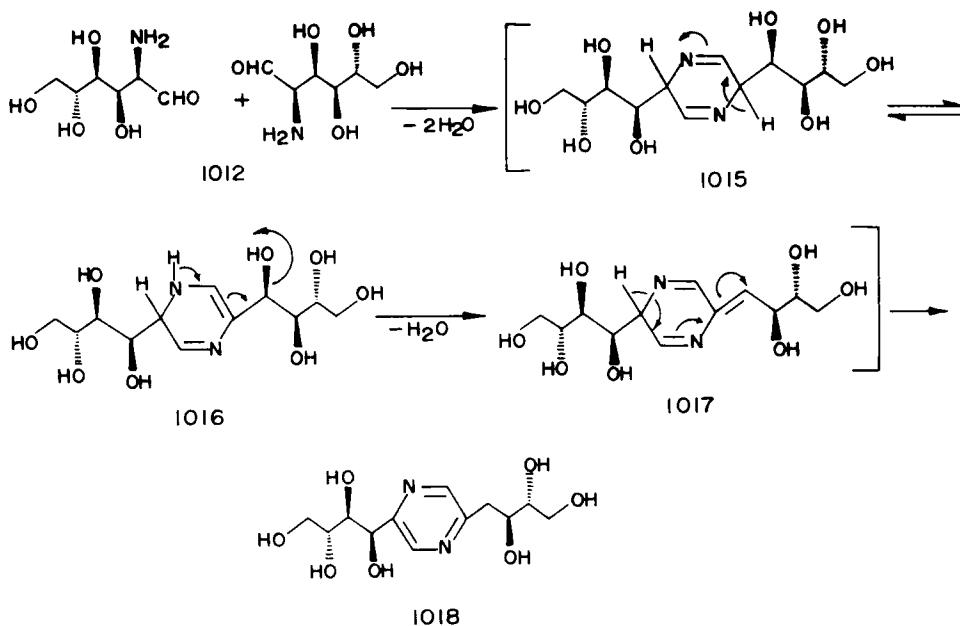
SCHEME 293

(66JOC2406) has also been reinvestigated. Compounds **1003** and **1004** were isolated from the mixture of products of the reactions and a mechanism for the formation of 2-(*D-arabino*-tetritol-1-yl)-5-(2-deoxy-*D-arabino*-tetritol-1-yl)pyrazine (**1018**) from 2-amino-2-deoxy-*D*-glucose (**1912**) was proposed (91CPB792) (Scheme 294).

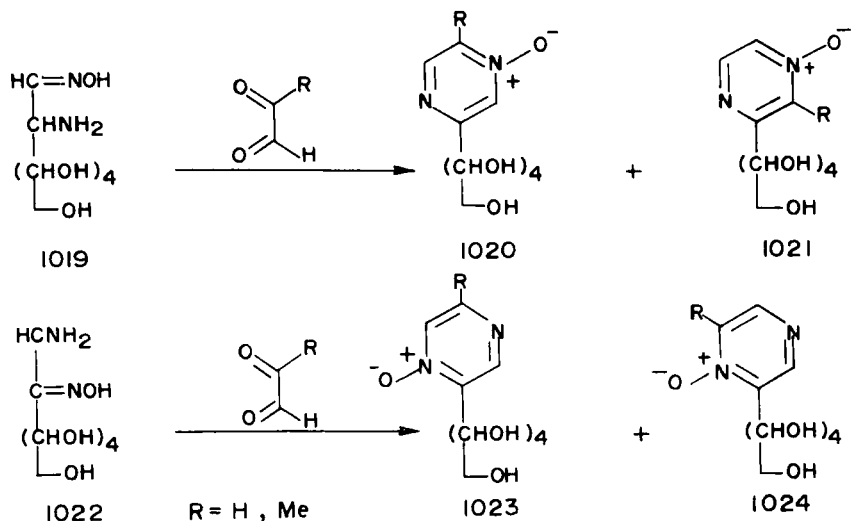
The pyrazine-4-oxide ring of the acyclo *C*-nucleosides **1020** and **1021** was constructed by cyclocondensation of 2-amino-2-deoxy-1-oximino derivatives of monosaccharides (**1019**) with glyoxal or methylglyoxal (69JOC3842; 72JOC2635; 82ABC2169; 80JOC1693). From the same reaction with the 1-amino-1-deoxy-2-oximino derivatives **1022**, the isomeric pyrazine-1-oxide acyclo *C*-nucleosides **1023** and **1024** were obtained (72JOC2635; 80JOC1693) (Scheme 295).

1,2-Diamino-1,2-dideoxy sugars (**1025**) cyclocondensed with benzil to give the dihydropyrazines **1026**, which were chemically dehydrogenated to **1027** (91MI15) (Scheme 296).

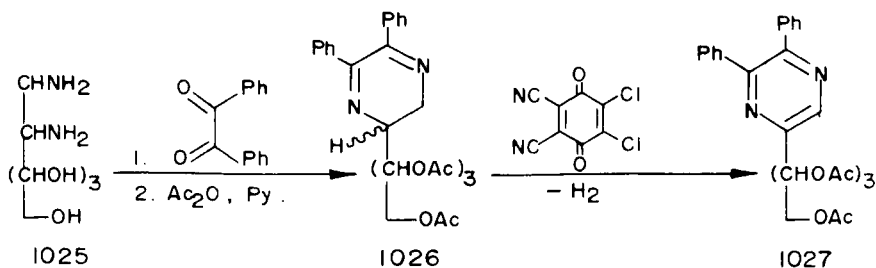
Separation and identification of the trimethylsilyl derivatives of various pyrazine acyclo *C*-nucleosides were studied using gas liquid chromatography-mass spectrometry (78MI12).



SCHEME 294



SCHEME 295



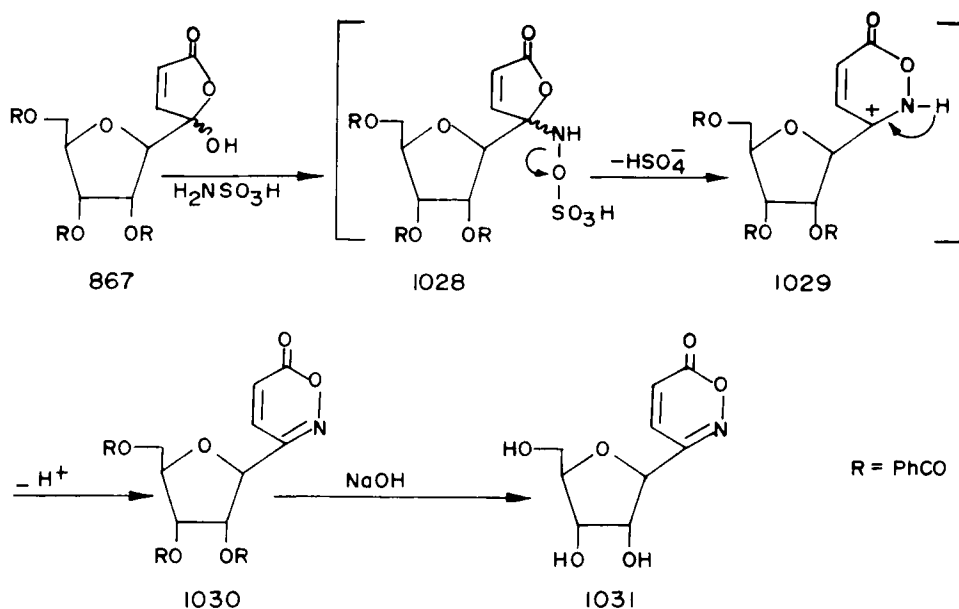
SCHEME 296

XXVII. 1,2-Oxazine C-Nucleosides

A. ISOXAZINE C-NUCLEOSIDES

1. 3-IsloxazinyI C-Nucleosides

The 5-hydroxy-5-(β -D-ribofuranosyl)furan-2-one derivative **867** underwent ring expansion when treated with hydroxylamino-*O*-sulfonic acid to give the 1,2-oxazin-3-yl C-nucleoside **1031** (87JOC4521) (Scheme 297).



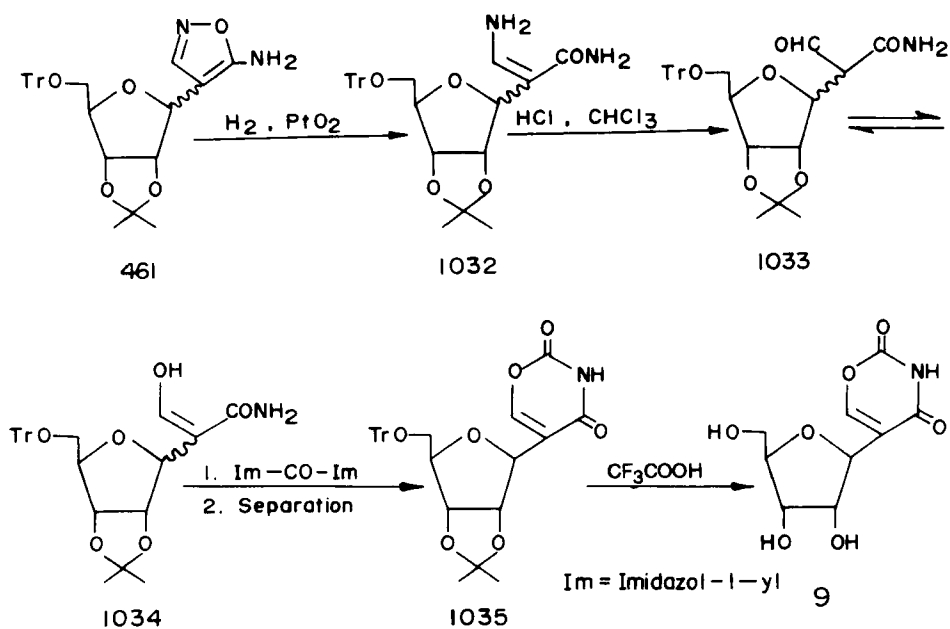
SCHEME 297

XXVIII. 1,3-Oxazine C-Nucleosides

A. THE NATURALLY OCCURRING C-NUCLEOSIDE ANTIBIOTIC "OXAZINOMYCIN"

A Japanese research group isolated oxazinomycin in 1970 from the culture filtrates of *Streptomyces tanesashinesis* (70MI7) and fully identified its structure as 5-(β-D-ribofuranosyl)1,3-oxazin-2,4-dione (**9**) depending on spectral and X-ray crystallographic data (71JAN797). Independently, and almost simultaneously, another Japanese group reported the isolation of an antibiotic named minimycin from the culture broth of *Streptomyces hygroscopicus* (70MI8), and its structure (71GEP2043946; 72JAN44, 72JAN151) was identical with that of oxazinomycin. Oxazinomycin was also reported to occur, associated with pyrazofurin (**7**), in cultures of *Streptomyces candidus* (75ANY544). It possesses activities against ascites and solid tumors in mice (71GEP2043946, 71JAN797; 72JAN44) and gram-positive and gram-negative bacteria (71JAN797; 72JAN44; 73JAP73/16198).

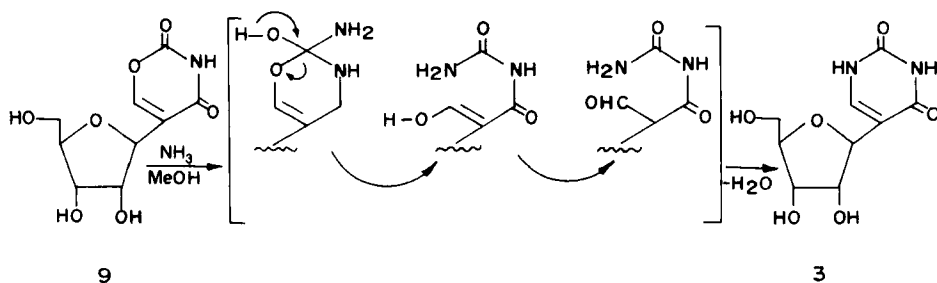
Oxazinomycin (**9**) was synthesized from the 4-isoxalyl C-nucleoside derivative **461** by the reaction sequence shown in Scheme 298 (77JOC109;



SCHEME 298

78USP4096321). 2',3'-*O*-Carbonyloxazinomycin was found to increase the survival rate of mice transplanted with leukemia cells [85JAP(K)85/169484].

Treatment of oxazinomycin (9) with ammonium hydroxide or ammonium carbonate caused its transformation into pseudouridine (3) according to the proposed mechanism outlined in Scheme 299 (72JAN151).



SCHEME 299

B. 1,3-OXAZINE C-NUCLEOSIDES

1. 1,3-Oxazin-2-yl C-Nucleosides

In addition to the previously mentioned spiro 1,3-oxazine C-nucleoside derivative **699** (85CPB102) (Section XIV, A; Scheme 187), the unsaturated 1,3-oxazin-2-yl C-nucleoside **1037** was prepared from the *S*-benzyl β -D-ribofuranosylthioformimidate derivative **1036** by reaction with diketene (85CPB102) (Scheme 300).

C. 1,3-OXAZINE CARBOCYCLIC C-NUCLEOSIDES

1. 1,3-Oxazin-5-yl Carbocyclic C-Nucleosides

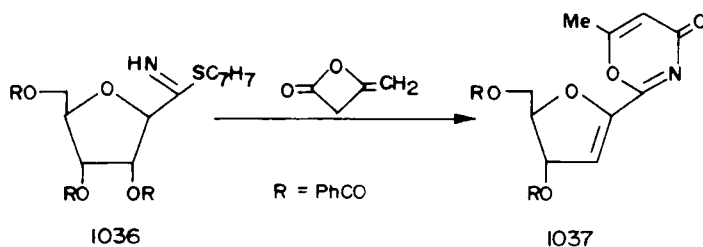
A total synthetic approach was devised for the preparation of the carbocyclic analog **1044** of oxazinomycin [87JCS(C)1422] as shown in Scheme 301.

D. 1,3-OXAZINE ACYCLO C-NUCLEOSIDES

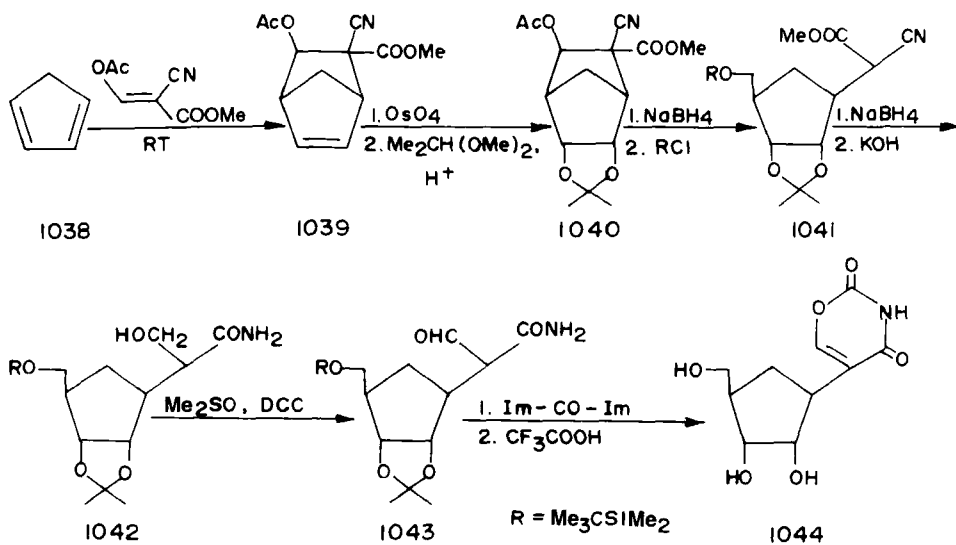
1. 1,3-Oxazin-6-yl Acyclo C-Nucleosides

Beckmann rearrangement of the D-mannono-1,4-lactone oxime derivative **1046**, obtained by oxidation of the *aldehydo*-D-mannose oxime derivative **1045**, with butyllithium followed by treatment with phosphorus pentachloride gave the 2-chloro-4,5-dihydro-1,3-oxazin-6-yl acyclo C-nucleoside **1047** (85HCA2254) (Scheme 302).

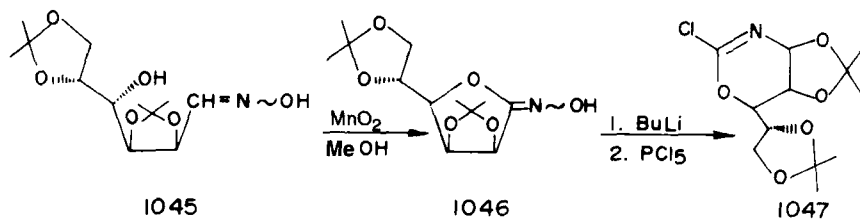
Base-catalyzed intramolecular displacement of the 4-*O*-methylsulfonyloxy group in the D-glucitol derivative **1048** by the carbonyl of the 2-butyloxycarbonylamino group afforded the 1,3-oxazin-6-yl C-nucleoside derivative **1050** (94T13299) (Scheme 303).



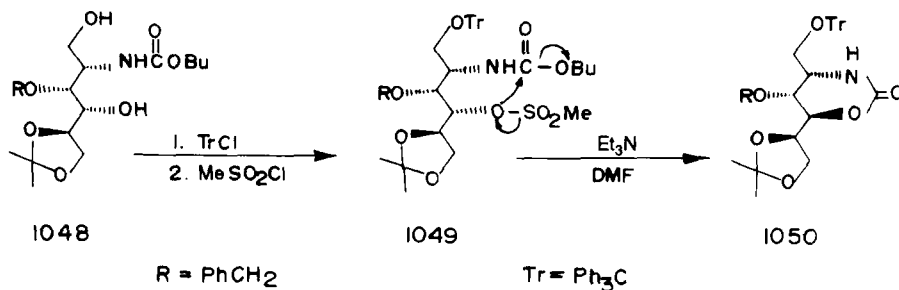
SCHEME 300



SCHEME 301



SCHEME 302



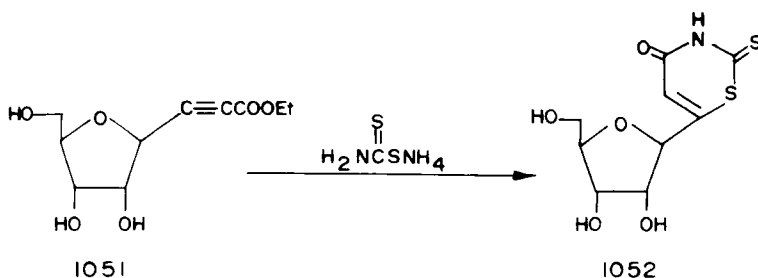
SCHEME 303

XXIX. 1,3-Thiazine C-Nucleosides**A. 1,3-THIAZINE C-NUCLEOSIDES****1. 1,3-Thiazin-6-yl C-Nucleosides**

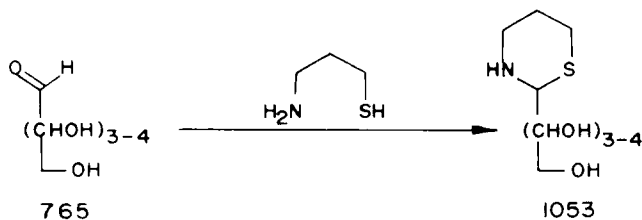
The only reported example of this class **1052** was obtained by the reaction of ethyl 3-(β -D-ribofuranosyl)propynoate **1051** with ammonium dithiocarbamate (75TL3271; 79JOC4854) (Scheme 304).

B. 1,3-THIAZINE ACYCLO C-NUCLEOSIDES**1. 1,3-Thiazin-2-yl Acyclo C-Nucleosides**

Reaction of aldopentoses or aldohexoses (**765**) with 3-aminopropanthiol gave the 2-(alditol-1-yl)tetrahydro-1,3-thiazines **1053** (62CB100) (Scheme 305).



SCHEME 304



SCHEME 305

XXX. 1,2,4-Triazine C-Nucleosides

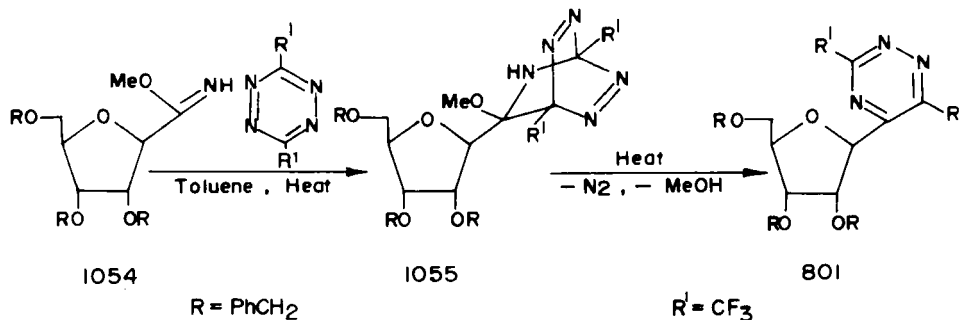
A. 1,2,4-TRIAZINE C-NUCLEOSIDES

1. 1,2,4-Triazin-5-yl C-Nucleosides

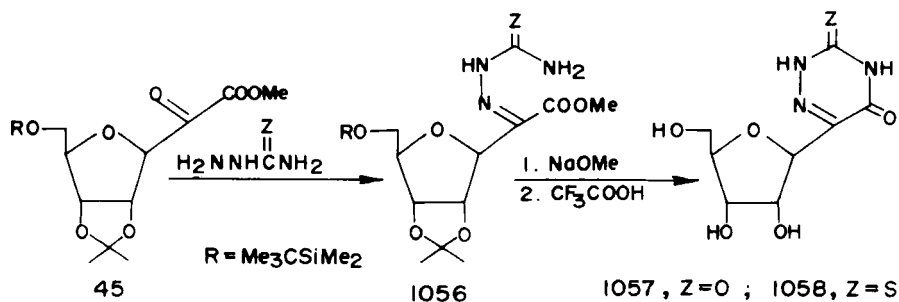
Inverse Diels–Alder cycloaddition of the β -D-ribofuranosyl formimide (**1054**) and 3,6-bis(trifluoromethyl)tetrazine formed the adduct **1055**, which then lost a nitrogen molecule to afford the 5-(β -D-ribofuranosyl)1,2,4-triazine C-nucleoside **801** (95AP175) (Scheme 306).

2. 1,2,4-Triazin-6-yl C-Nucleosides

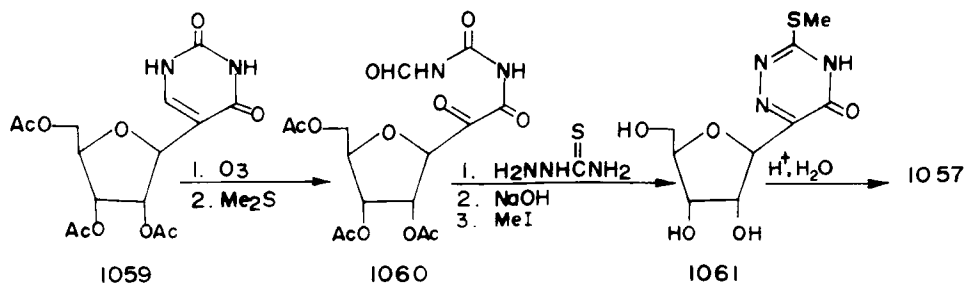
Condensation of the methyl 2-(β -D-ribofuranosyl)-2-oxoacetate **45** with semicarbazide or thiosemicarbazide gave the corresponding semicarbazone **1056**, which cyclized with sodium methoxide to the 6-(β -D-ribofuranosyl)-1,2,4-triazine-3,5-dione **1057** or its 3-thione **1058** (78TL1829; 84BCJ2515) (Scheme 307).



SCHEME 306



SCHEME 307



SCHEME 308

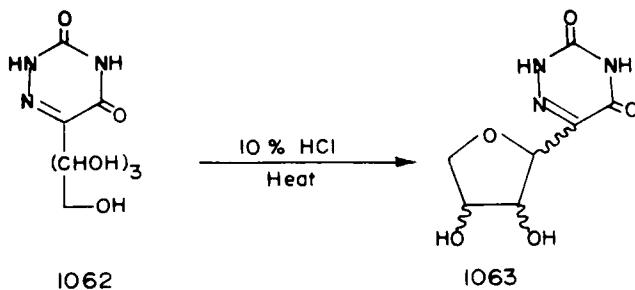
The C-nucleoside **1057** has also been prepared by modification of 2', 3', 5'-tri-*O*-acetyl pseudouridine (**1059**) according to the steps shown in Scheme 308 (68TL1543; 69CCC1690).

6-(Tetritol-1-yl)-1,2,4-triazines (**1062**) (Section XXX,D) underwent cyclodehydration by heating with dilute hydrochloric acid to the corresponding 1,2,4-triazin-6-yl C-nucleosides **1063** (66CCC1414; 67CCC3572) (Scheme 309).

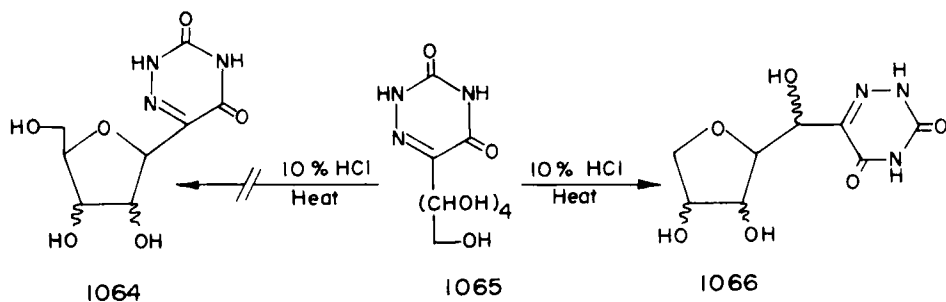
B. 1,2,4-TRIAZINE HOMO C-NUCLEOSIDES

1. 1,2,4-Triazin-6-yl Homo C-Nucleosides

The 1,2,4-triazine homo C-nucleosides prepared so far are the 1,2,4-triazin-6-yl type. Acid-catalyzed dehydrative cyclization products of the polyhydroxyalkyl chains of 6-(alditol-1-yl)1,2,4-triazines (**1065**) (Section XXX,D) were first assigned the corresponding 6-(β -glycofuranosyl)-1,2,4-



SCHEME 309



SCHEME 310

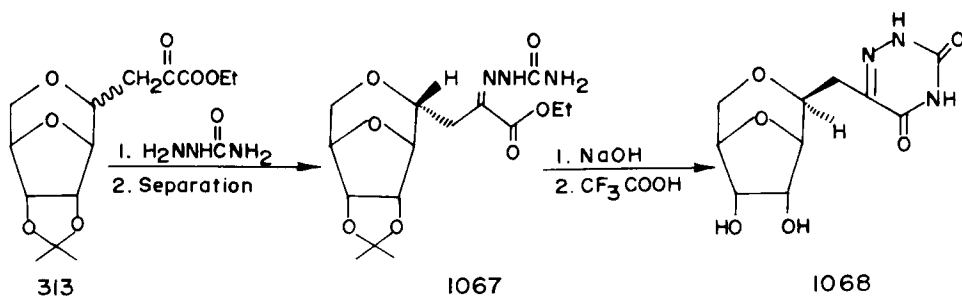
triazole structures **1064** (66CCC1414, 66TL3115). Later, ¹H NMR spectral studies revealed that the products are the 1,2,4-triazin-6-yl homo C-nucleosides **1066** (68TL1543; 69CCC1673) (Scheme 310).

The 1,2,4-triazin-6-yl homo C-nucleoside derivative **1068** was obtained by cyclization of the semicarbazone **1067** derived from the α-keto ester **313** (76CJC2940) (Scheme 311).

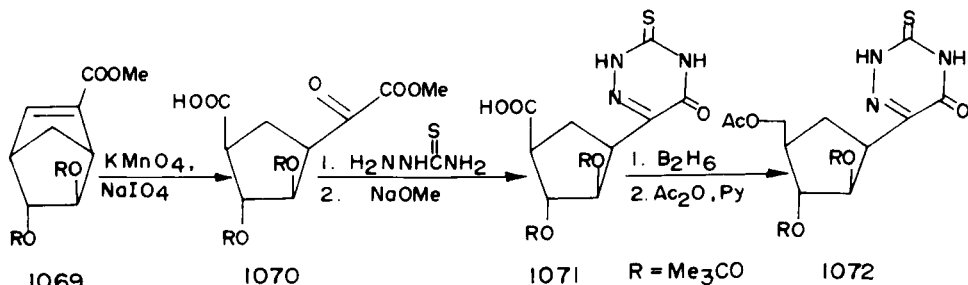
C. 1,2,4-TRIAZINE CARBOCYCLIC C-NUCLEOSIDES

1. 1,2,4-Triazin-6-yl Carbocyclic C-Nucleosides

Only 1,2,4-triazin-6-yl carbocyclic C-nucleosides are known. The steps shown in Scheme 312 were devised as a total synthetic approach for the preparation of the 1,2,4-triazine carbocyclic C-nucleoside **1072** (76CJC2925). A similar reaction route was used for the synthesis of **1072** having different hydroxyl configurations [77CJC427; 81JCS(P1)2299].



SCHEME 311



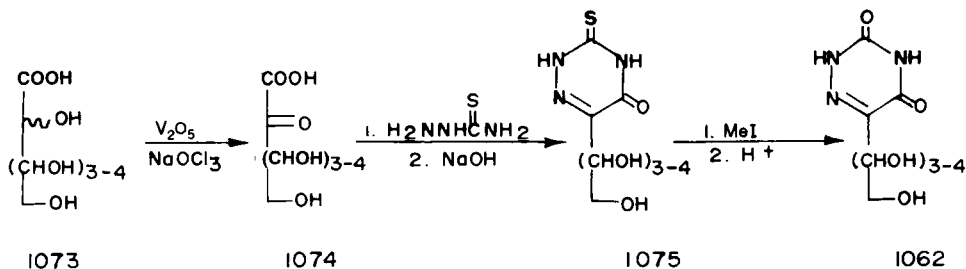
SCHEME 312

D. 1,2,4-TRIAZINE ACYCLO C-NUCLEOSIDES

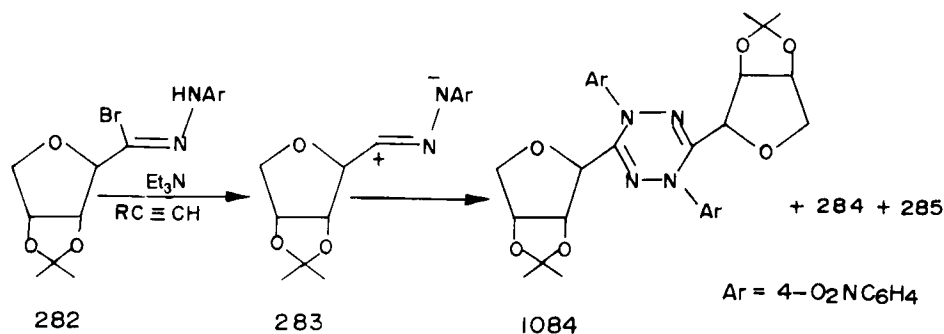
1. 1,2,4-Triazin-6-yl C-Nucleosides

Thiosemicarbazones of aldoses-2-ulosonic acids **1074** are cyclizable with alkali to the corresponding 6-(alditol-1-yl)-5-oxo-3-thioxo-1,2,4-triazines (**1075**), which were desulfurized to the 1,2,4-triazin-3,5-dione acyclo C-nucleosides **1062** (66CCC1414, 66TL3115; 67CCC3572; 69CCC1673) (Scheme 313).

The synthesis of 5- and 6-(alditol-1-yl)-3-amino-1,2,4-triazines was studied in connection with the inhibition of the biologically important Maillard browning reaction of sugars by aminoguanidine. When treated with aminoguanidine at physiological conditions, aldoses-2-uloses (2-ketoaldoses or sugar osones) (**1076**) or their 3-deoxy analogs (**1078**) gave **1077** in the case of aldoses (**1075**) (92MI7) and a mixture of **1079** and **1080** in the case of 3-deoxyaldoses (**1078**) (91MI16; 92MI7, 92MI8; 93MI10) (Scheme 314).



SCHEME 313



SCHEME 316

ACKNOWLEDGMENT

The authors are very grateful to Zaki M. El-Shafei for proofreading the manuscript.

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 44JOC470
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